7

Helminth Infection

Kenneth S. Warren, D. A. P. Bundy, Roy M. Anderson, A. R. Davis, Donald A. Henderson, Dean T. Jamison, Nicholas Prescott, and Alfred Senft

In "This Wormy World," published in 1947, N. R. Stoll estimated that there were more than 2,200 million human helminthic infections (cestodes, 72 million; trematodes, 148 million; nematodes, 2,000 million) in a world which contained 2,166 million people. Since then the world's population has more than doubled, but the proportion infected with different worm species remains almost unchanged. Approximately twenty major helminth species infect humans; table 7-1 provides both the scientific and common names of the organisms as well as the mode of infection and the principal disease manifestations. An examination of the prevalence, mortality, and morbidity of the primary infectious diseases of Africa, Asia, and Latin America ranked schistosomiasis fifth, hookworm tenth, onchocerciasis twelfth, ascariasis fifteenth, trichuriasis twenty-first, and filariasis twenty-second (Walsh and Warren 1984).

Such has been the concern about these infections that the first significant global campaign to attempt to eradicate any infectious disease was focused on hookworm (Fosdick 1952). It was considered to be an "anemia-producing disease which sapped vitality and handicapped, crippled, and even killed millions of men, women, and children in the hot, moist regions of the world." When the campaign began in 1913 it soon became apparent that it would not be possible to eradicate infection or even to control transmission. As the campaign progressed, however, it was realized that although infection was uncontrollable, disease could be prevented simply and rapidly by the reduction of worm burdens, even with the poor anthelmintic drugs then available. Unfortunately, not only was this unique strategy forgotten, but hookworm infection remains uncontrolled, there being today approximately 900 million infections.

Seventy-five years later, in 1988, an international symposium on hookworm reexamined these issues and concluded with the question, What can we do now? (Warren 1989). It then became apparent that the ineffective, toxic drugs of the past have been superseded by effective nontoxic, oral, single-dose, broad-spectrum benzimidazole anthelmintics that can treat not only hookworm infection but the other main geohelminthiases, ascariasis and trichuriasis, as well. Furthermore, the multispecies approach could be extended by including other broad-spectrum anthelmintics, such as praziquantel (PZQ), which is effective against virtually all the trematode and cestode infections, and ivermectin (IVR) for the filariases and strongyloidiasis (Warren 1989). Thus, it has now become possible to treat virtually all the major helminthic infections with single-dose, orally administered, relatively nontoxic drugs.

Advances in our understanding of the transmission characteristics of these parasites have also made a significant contribution to the development of more rational control strategies. Helminths are unique among infectious agents, including protozoa, bacteria, viruses, and fungi, in that, with very few exceptions, they do not multiply in their human definitive hosts. As each worm is the result of a separate infection event, reducing the number of infections reduces the worm burden and hence the morbidity. Furthermore, helminths have a clustered, overdispersed distribution in human populations such that only a small proportion of infected individuals harbor heavy worm burdens; it is within this intensely infected group that most of the morbidity and mortality occur. These findings suggest that a strategy is feasible in which helminth-induced disease can be prevented merely by keeping worm burdens at a low level. Because in most cases the rate of acquisition of infection is low, it may take many months or years for the burdens to reach disease-producing levels. This implies that treatment can be administered to reduce disease at much less frequent intervals than to reduce infection. Thus, a form of mass prophylaxis can be instituted in which infection (transmission) is not specifically targeted but disease is largely eliminated.

Another aspect of this strategy is that prophylaxis can be directed toward those groups of individuals with the highest degree of exposure and the heaviest worm burdens. With many of the helminthic infections the most vulnerable group is school-age children. Treatment of this age group offers the possibility not only that concurrent disease manifestations may be prevented but also that future consequences of chronic childhood infection (such as hepatosplenic disease in schistosomiasis, elephantiasis in filariasis, and blindness in oncho-

Table 7-1. Major Helminth Infections in Humans

Organism	Common name	Means of infection	Major disease manifestation[a]
Nematodes (roundworms)			
Ancylostoma duodenale, Necator americanus	Hookworm	Skin	Anemia
Ascaris lumbricoides	Giant roundworm	Oral	Intestinal obstruction
Dracunculus medinensis	Guinea worm	Oral	Cutaneous lesions
Enterobius vermicularis	Pinworm	Oral	Anal pruritus
Onchocerca volvulus	River blindness	Insect	Blindness
Strongyloides stercoralis	Strongyloidiasis	Skin	Autoinfection
Trichinella spiralis	Trichinosis	Oral	Myositis
Trichuris trichiura	Whipworm	Oral	Rectal prolapse
Wuchereria bancrofti, Brugia malayi	Filariasis	Insect	Elephantiasis
Trematodes			
Clonorchis sinensis, Opisthorchis viverrini, O. felineus	Liver fluke	Oral	Biliary obstruction
Fasciola hepatica	Liver fluke	Oral	Hepatomegaly
Fasciolopsis buski	Intestinal fluke	Oral	Diarrhea
Paragonimus westermani	Lung fluke	Oral	Cough
Schistosoma hematobium	Blood fluke	Skin	Hydronephrosis
Schistosoma japonicum, S. mansoni	Blood fluke	Skin	Hepatosplenomegaly
Cestodes			
Diphyllobothrium latum	Fish tapeworm	Oral	Anemia
Echinicoccus granulosus	Hydatid	Oral	Cyst
Tenia saginata	Beef tapeworm	Oral	None
Tenia solium	Pork tapeworm	Oral	Cysticercosis

a. These manifestations are relatively infrequent and tend to be related to the intensity of infection. Exceptions are dracunculiasis, strongyloidiasis, and echinococcosis.
Source: Authors.

cerciasis) will be ameliorated. In addition, the reduction in worm burdens in a heavily infected group will often reduce the rate of infection to others and hence reduce overall parasite transmission in the community. Of those few helminths that are particularly resistant to pharmacological agents, *Trichinella spiralis*, *Fasciola hepatica*, and *Dracunculus medinensis*, the latter is particularly worthy of mention as a prime candidate for global eradication, in which effort a variety of public health measures would be used (Hopkins and Ruiz-Tiben 1990).

Recent advances in our understanding of the public health consequences of helminthic infections suggest that attempts to control morbidity are now urgently required. Contrary to the earlier perception, it is not the acute effects of infection which are the primary public health concern but the chronic and insidious effects of continuous infection throughout childhood. This has implications not only for the growth and intellectual development of the affected child, but also for the subsequent well-being of the adult.

It is timely, then, for these reasons, to reassess both the priority that disease control should claim and the nature of the control strategies to be employed. Our purpose in this chapter is to begin that reassessment. First we describe helminthic infections and then turn to an assessment of their global public health significance. We go on to present potential strategies for control (vaccination, vector control, improved hygiene, and chemotherapy and chemoprophylaxis), after which we discuss the potential for an integrated strategy for chemoprophylactic control of helminthic infections; and finally, we present our conclusions.

Public Health Significance of Helminth Infections

This section describes the geographical distribution of helminthic infections and then examines the public health consequences of these infection patterns.

Geographical Distribution

Current estimates suggest that more than a third of the world's population is infected with one or several species of parasitic worm and that these are among the most prevalent infections of humans (table 7-2). Although it is clear that the number of infections is very large, the precision of such estimates is rather crude because information is lacking for many areas. An error of a few percentage points in estimating the prevalence of infection in China, for example, with approximately one-quarter of the world's population, may result in an over- or underestimate of tens of millions of cases (Young and Prost 1985).

This margin of error is even greater when morbidity is considered. Very few studies include estimates of the intensity of infection, yet it is primarily the size of the worm burden which determines the morbid consequences of infection. Data on morbidity are notoriously more difficult to obtain than on

Table 7-2. Estimates of Number of Helminth Infections
(millions)

	Market economies	Nonmarket economies	South and Central America	Middle East and North Africa	Sub-Saharan Africa	Indian subcontinent	China	Asia (excluding Indian subcontinent and China)	Total
Nematodes									
Ascaris	4	30	150	55	45	160	510	175	1,129
Brugia	0	0	0	0	0	10	55	35	100
Hookworm	0.7	6	95	50	60	160	325	180	876.7
Onchocerca	0	0	0.1	2	16	0	0	0	18.1
Trichinella	4	2	4	1	..	..	..	..	11
Trichuris	2	45	110	20	30	70	320	170	770
Wuchereria	0	0	4	15	30	40	45	50	184
Trematodes									
Clonorchis	0	0	0	0	0	0	0	0	32
Fasciolopsis	0	0	0	0	0	0	0	0	17
Paragonimus	0	0	..	0	0	0	0	..	6
Schistosoma hematobium	0	0	0	30	70	0	0	0	100
Schistosoma intercalatum	0	0	0	0	12	0	0	0	12
Schistosoma japonicum	0	0	0	0	0	0	10	85	95
Schistosoma mansoni	0	0	14	20	35	0	0	0	69
Schistosoma mekongi	0	0	0	0	0	0	0	0.6	
Cestodes									
Diphyllobothrium	0.1	5	..	0	0	0	0	4	9.1
Tenia saginata	1	30	2	0	30	0	0	10	73
Tenia solium	..	1	1	0	1	0	0	3	5

0 represents very low prevalence of helminths and no reports of high prevalence.
.. Focal records, low prevalence.

Note: Estimates of morbidity ae generally unavailable for helminthiases. Estimates from Walsh (1984) suggest the following number of clinical cases of schistosomiasis: *S. mansoni*, 3.3 million; *S. hematobium*, 4.9 million; *S. japonicum*, 4.7 million; *S. intercalatum*, 0.6 million; *S. mekongi*, 30,000. There are an estimated 336,400 cases of blindness from onchocheriasis (WHO 1987).

Source: The data for geohelminths, lymphatic filariasis, and schistosomiasis are derived from a survey of the original literature. Data on onchocerciasis are from WHO 1987. All other estimates are based on secondary sources (Stoll 1947; Le Riche 1967; Peters 1978; WHO 1981, 1984, 1987; Warren and Mahmoud 1984).

mortality. Carefully conducted studies, however, have shown a relationship between infection intensity and clinical effects.

The geohelminths are the most ubiquitous of the major human helminthiases. *Ascaris lumbricoides* and the slightly less prevalent *Trichuris trichiura* occur worldwide in almost any community which is socioeconomically depressed. The distribution is limited by extremes of temperature and humidity but extends well beyond the tropics into northern and southern temperate zones (Crompton 1989). Current estimates by the World Health Organization (WHO) are 1,000 million *Ascaris* and 750 million *Trichuris* infections. Although these estimates of infection in table 7-2 are probably low, diseases or morbidity are also believed to be significantly underestimated (Pawlowski and Davis 1989; Bundy and Cooper 1989), largely because the chronic effects on growth and development in children are grossly underreported. In one study of trichuriasis, for example, only 2 percent of actual cases were represented in health statistics (Cooper, Bundy, and Henry 1986). Such underreporting may have led to the commonly quoted misconception that trichuriasis is of public health significance only in restricted regions, a perception that has been refuted by the accumulation of evidence of morbidity from a broad range of tropical locations. The estimate that 10 percent of all infections are sufficiently intense to affect growth and development, although not necessarily to cause overt clinical signs, suggests that more than 100 million people may suffer some morbidity from geohelminthic infections alone.

The two important hookworm species *Ancylostoma duodenale* and *Necator americanus* together have a circumequatorial distribution. Still, this is more restricted than that of the other geohelminths, and the hookworms are less commonly found outside the true tropics. The World Health Organization estimates that there are currently 900 million infections. The main morbidity is associated with anemia, involving both adults and children (Migasena and Gilles 1987; Schad and Warren 1989).

The pinworm, *Enterobius vermicularis*, still occurs commonly in temperate regions, where it is the most prevalent helminthiasis. It is now recognized that this worm is also common in tropical regions, although its true prevalence is unknown, largely because diagnosis of infection requires a technique, anal swabbing, which is not often employed in mass surveys. Infection is rarely associated with significant morbidity.

The filarial nematodes are almost exclusively tropical, and only *Wuchereria bancrofti* has a global distribution. *Brugia malayi* is confined to Asia, where the infection occurs in the

Malaysian peninsula, some areas of the Philippines, and Indonesia, as well as in foci in India and China (CIBA Foundation 1987). The World Health Organization estimates that there are currently 90 million infections, almost half of which (40 million) occur in India. The estimates in table 7-2 are significantly higher, even if the data for China (see caveat above) are excluded. Morbidity refers mainly to adult disablement due to elephantiasis. The number of cases afflicted by the less obvious, but functionally disabling, effects of episodic filarial fever is unknown.

Onchocerca volvulus is focal in West and Central Africa, in northern South America, and in Central America. It is the subject of major control efforts in West Africa. Although the condition is rarely fatal, it is severely disabling, because the main morbid consequence is blindness.

The guinea worm, *Dracunculus medinensis*, occurs in limited foci in arid habitats in India, Pakistan, and (currently) seventeen countries of Sub-Saharan Africa. This infection may be declining as a result of control efforts. It is estimated by WHO that there are currently 10 million cases globally, all of which are potentially disabling and have an attendant risk of severe morbidity due to secondary infection.

Strongyloides stercoralis occurs circumglobally in tropical and subtropical areas but is also of importance in the temperate regions because of the persistence of chronic relapsing infection in cases acquired elsewhere and because of endemic infection in specific foci (particularly, institutions). The true prevalence is unknown because of the difficulty in diagnosing subclinical infection. The actual morbidity is also unknown but is likely to be considerable, because most of the reported infections represent clinical cases (Grove 1989).

Trichinella spiralis is primarily an infection of temperate regions and is one of the few human nematodiases which is declining in prevalence, primarily because of improved food hygiene. Infection may be associated with severe morbidity.

Of the schistosomes, only *Schistosoma mansoni* has spread into the Americas, where the infection is endemic in large tracts of Brazil and in limited foci in Venezuela and the Caribbean islands. *S. mansoni* also remains endemic in much of West and East Africa, overlapping throughout most of this area with *S. hematobium*, which has a range extending further to the northeast and southwest. The distribution of both parasites encompasses the limited foci of *S. intercalatum* in Central and West Africa. *S. japonicum* predominantly occurs in China, the Philippines, and Indonesia. There may also be small foci in Malaysia, Thailand, Laos, and Cambodia, where there is overlap with the distribution of *S. mekongi*. The distribution has recently been described in detail (WHO 1987a), and it is estimated that there are currently 200 million cases. The clinical consequences of the various forms of schistosomiasis are well established and may be associated with significant morbidity (WHO 1985; Mott 1988), although precisely defining the extent of the morbidity has proven problematical (Morrow 1984). The estimates in table 7-2 are based on those of Walsh and Warren (1984), which some consider an overestimate.

Other digenean parasites of human health importance are *Clonorchis sinensis*, *Fasciolopsis buski*, and *Paragonimus westermani*. These are confined largely to Asia, where they may be associated with significant disease (Rim 1986).

Tenia saginata infection is endemic in pastoral communities in Africa, in urban communities in the area that was formerly Eastern Europe, and in both in Latin America. Epizootics occur in North America. The clinical effects are mild. In contrast, *T. solium* infection is much less common, is more closely associated with socioeconomically depressed communities, and may result in severe neurological symptoms. The prevalence of this disease may be underestimated, because the foci in Latin America are now recognized to be larger than had been assumed.

The fish tapeworm, *Diphyllobothrium latum*, is characteristic of northern temperate regions. Control measures have achieved significant declines in prevalence.

Echinococcus granulosus infection occurs wherever there are suitable domestic animal hosts, and it therefore has a global distribution which includes both tropical and temperate regions. Global prevalence data are unavailable, but human infection is associated with severe, sometimes fatal, clinical effects.

Consequences of Helminthic Infections

Helminthic infections may produce a range of diverse consequences: from impairment of the growth and development of children, to reducing the functioning of schoolchildren in educational institutions, and even their ability to attend school; from very low levels of impairment of the day-to-day function of adults to significant inhibition of productivity; from mild to severe acute morbidity (for example, anemia) to death (from, for example, intestinal obstruction); and from severe chronic disability (for example, blindness and elephantiasis) to death (from, for example, bleeding esophageal varices). As to mortality per se, only schistosomiasis generates a substantial burden (Walsh 1990); even that burden, however, is but a fraction of deaths in the developing world due to diarrheal disease, acute respiratory infections, and measles. The principal public health significance of the helminthiases resides, then, not in their effect on mortality but, rather, in their consequences of impaired growth and development in children, chronic disability, and long-term impairment of function. These consequences, combined with the extremely high prevalence of many helminthic infections, suggest aggregate outcomes for these conditions that are very substantial from the standpoint of both economic productivity and general welfare.

Our purpose in this section is to point out the available literature on the effect of helminthiases on disability, malnutrition, and functional impairment. For a few of the topics to be reviewed there is substantial literature, sometimes with useful and up-to-date reviews—for example, the reviews by Stephenson (1987) and Holland (1987a, 1987b) of the effect of helminths on nutrition and the review by Andreano and

Helminiak (1988) of, among other things, the effect of schistosomiasis on labor productivity. By and large, however, the literature is more notable for its gaps than its well-defined conclusions. For that reason this summary will draw more than we would like on anecdotal and clinical accounts, on plausible inferences, and on reports of associations that are potentially confounded by a range of extraneous variables. This "soft" literature is importantly suggestive; it in no way replaces but rather underlines the need for harder research in the future. Before turning to that literature, however, we provide brief descriptions of the nature of the infections and the associated morbidity and mortality.

ACUTE MORBIDITY AND MORTALITY. The major helminthic parasites of humans enter the body in a variety of ways: orally, by direct penetration of the skin, and by injection by biting insects (table 7-3). The invading organisms may undergo a variety of metamorphoses while in the body and may migrate through multiple organ systems to reach their preferred sites (table 7-3). The metamorphoses and migration routes provide insight into the ways by which these parasites cause disease and into the localization of signs and symptoms. It must also be borne in mind that in many parts of the developing world, people, particularly children, harbor multiple parasitic worms simultaneously. Thus, on the east coast of Kenya, children will frequently carry *Ascaris*, *Trichuris*, hookworm (the geohelminths), schistosomes, filariae, and the beef tapeworm. In western Africa, onchocerciasis and dracunculiasis may be added. In the northeast of Thailand, children will carry all the geohelminths, *Opisthorchis*, and perhaps *Fasciolopsis*. Colombians will harbor, in addition to the geohelminths, *Onchocerca*, the pork tapeworm with its attendant danger of cysticercosis and, possibly, *Fasciola*. Inuit children will often carry *Trichinella*, *Diphyllobothrium*, and *Echinococcus*. All the above individuals may also have enterobiasis and strongyloidiasis.

Table 7-3. Migration Pathways of Helminths in Humans

Organism	Pathway
Nematodes	
Ancylostoma (Necator)	Skin–lungs–small intestines
Ascaris	Mouth–intestines–lungs–small intestine
Dracunculus	Mouth–intestines–subcutaneous tissues
Onchocerca	Insect bite–connective tissues–skin and eyes
Strongyloides	Skin–lungs–small intestine
Trichinella	Mouth–small intestine musculature
Trichuris	Mouth–large intestine
Wuchereria (Brugia)	Insect bite–lymph nodes–blood
Trematodes	
Clonorchis (Opisthorchis)	Mouth–intestines–bile ducts
Fasciola	Mouth–intestines–liver–bile ducts
Fasciolopsis	Mouth–small intestine
Paragonimus	Mouth–small intestine–lung and brain
Schistosoma hematobium	Skin–lungs–vesical venules (bladder/ureters)
Schistosoma japonicum, *S. mansoni*	Skin–lungs–mesenteric venules (liver)
Cestodes	
Diphyllobothrium	Mouth–small intestine
Echinococcus	Mouth–small intestine–liver and lungs
Tenia saginata	Mouth–small intestine
Tenia solium	Mouth–small intestine

Source: Authors.

As previously observed, most helminths do not multiply in the human definitive host, and intensity of infection may vary from minimal numbers of worms to hundreds and, at times, thousands. Disease manifestations are closely related to intensity of infection; those with low worm burdens essentially have no signs or symptoms of infection.

When worm larvae penetrate through the skin or migrate within it they may cause a pruritic rash which can be quite severe (hookworm, *Strongyloides*, schistosomes). On oral ingestion and larval penetration into the bowel wall there may be transient intestinal symptoms (*Ascaris*, *Trichinella*, *Fasciola*, *Paragonimus*). During migration through the tissues eosinophilia will often occur (hookworm, *Ascaris*, *Trichinella*, filariae, *Strongyloides*, *Fasciola*, schistosomes). Migration through the lungs can lead to a transient pneumonitis (hookworm, *Strongyloides*, *Ascaris*).

The final site of the adult worms, however, plays the most important role in the development of most of the disease syndromes. These will now be described for each of the helminths found in table 7-1.

Nematodes

- *A. duodenale*, *N. americanus*. These organisms are attached to the mucosa of the small intestines and ingest 0.03–0.26 milliliters of blood per worm per day. The main manifestations of disease are iron-deficiency anemia and hypoalbuminemia. In heavy infections symptoms include fatigability, headache, numbness and tingling, dyspnea, palpitations, anorexia, dyspepsia, pedal edema, and sexual dysfunction. Signs include pallor and tachycardia.
- *Ascaris*. These large roundworms are free in the small intestines, and heavy worm burdens are associated with malnutrition, growth deficits, and impaired physical fitness. Masses of intertwined worms may cause intestinal obstruction, and single worms may obstruct the bile duct.
- *Dracunculus*. The long (30-centimeter), thin worms form burrows in the subcutaneous tissues, largely of the legs. When they reach maturity a blister occurs which bursts to release vast numbers of larvae. This is accompanied by itching and intense pain. Secondary bacterial infection of the worm tract is common.
- *Enterobius*. The main symptom of the presence of the worms in the perianal area is pruritis.
- *Onchocerca*. The adult worms are found in nodules in skin, muscles, and joint tissues. Larvae released from the

female adults migrate in the skin, where they may cause severe pruritic dermatitis. Larval migration within the ocular tissues may result in keratitis and chorioretinitis, leading to blindness and often, therefore, to premature death.

- *Strongyloides*. Although these organisms reside in the small bowel, they may revert to infectious forms, penetrating the skin to initiate an autoinfectious cycle. Intestinal symptoms include epigastric pain and diarrhea. Skin manifestations include urticaria and a pruritic, papular, erythematous rash. The disseminated form of infection, often seen in immunocompromised hosts, may result in fatalities.
- *Trichinella*. During acute infection diarrhea may be present. Manifestations from the invasion of muscle include fever, periorbital edema, and myalgia.
- *Trichuris*. There are two manifestations; in heavy infections there is anemia, prolapse of the rectum, and chronic colitis; in more moderate infections the colitis is associated with growth stunting.
- *Wuchereria, Brugia*. Acute inflammatory reactions, including lymphangitis or lymphadenitis, funiculitis, epididymitis, and orchitis, may occur, accompanied by headache, backache, and nausea. In chronic infections there may be hydrocoeles and elephantiasis.

Trematodes

- *Clonorchis, Opisthorchis*. Manifestations due to bile duct obstruction include fever, abdominal pain, and jaundice.
- *Fasciola*. Acute manifestations include fever, abdominal pain, hepatomegaly, asthenia, and urticaria. Manifestations of bile duct obstruction are very rare.
- *Fasciolopsis*. In heavy infections abdominal pain, diarrhea, and facial edema may be present.
- *Paragonimus*. Cough and hemoptysis may be found, as well as chest pain and profuse expectoration. Cerebral involvement may be accompanied by epilepsy, and signs of space-occupying lesions.
- *Schistosoma*. In S. *hematobium* infections there may be hematuria, dysuria, and renal failure plus an increased risk of cancer of the bladder. In S. *japonicum* and S. *mansoni*

Table 7-4. Disability and Nutritional Consequences of Helminth Infections

Infection	*Disability*	*Malnutrition*	
		PEM and growth retardation	*Anemia*
Nematodes			
Hookworm	n.a.	Little effect on macronutrient absorption except, possibly, some protein loss[a]	Major consequence of hookworm infection
Ascaris	n.a.	Growth faltering, reversible by intervention. Mechanisms may include protein loss and lactose malabsorption[a]	n.a.
Dracunculus	Mobility constraints for up to thirty weeks	n.a.	n.a.
Onchocerca	Blindness; severe sustained itching	n.a.	n.a.
Strongyloides	n.a.	Suggestive studies point to growth retardation and, possibly, protein deficiency	n.a.
Trichuris	Persistent colitis in some cases	Can cause substantial (but reversible) growth retardation[a]	Probably important in heavy infections
Lymphatic filaria	Severe mobility constraints and discomfort from elephantiasis	n.a.	n.a.
Trematodes			
Schistosomes	Decreased work capacity in heavy infections	Growth faltering due to S. *hematobium* and S. *japonicum*; mechanisms may include protein loss and altered endocrine function	Some evidence that S. *hematobium* causes anemia; anecdotal accounts also implicate S. *mansoni* and S. *japonicum*
Cestodes			
Tenia solium	Long-term mental impairment, sometimes involving epilepsy, from neural cysticercosis	n.a.	n.a.

n.a. Not applicable.

a. Studies with broad-spectrum chemoprophylaxis for hookworm, *Ascaris*, and *Trichuris* infections have revealed marked increments in growth.

Source: Cooper and Bundy 1986, 1987, and 1988; Cooper and others 1989; Crompton 1986; El Karim and others 1980; Holland 1987a; Holland 1987b; McGarvey and others 1990; Smith and others 1989; Stephenson 1987; Stephenson and others 1989; Tanner and others 1987.

infections there may be hepatomegaly, splenomegaly, bleeding esophageal varices, and cor pulmonale.

Cestodes

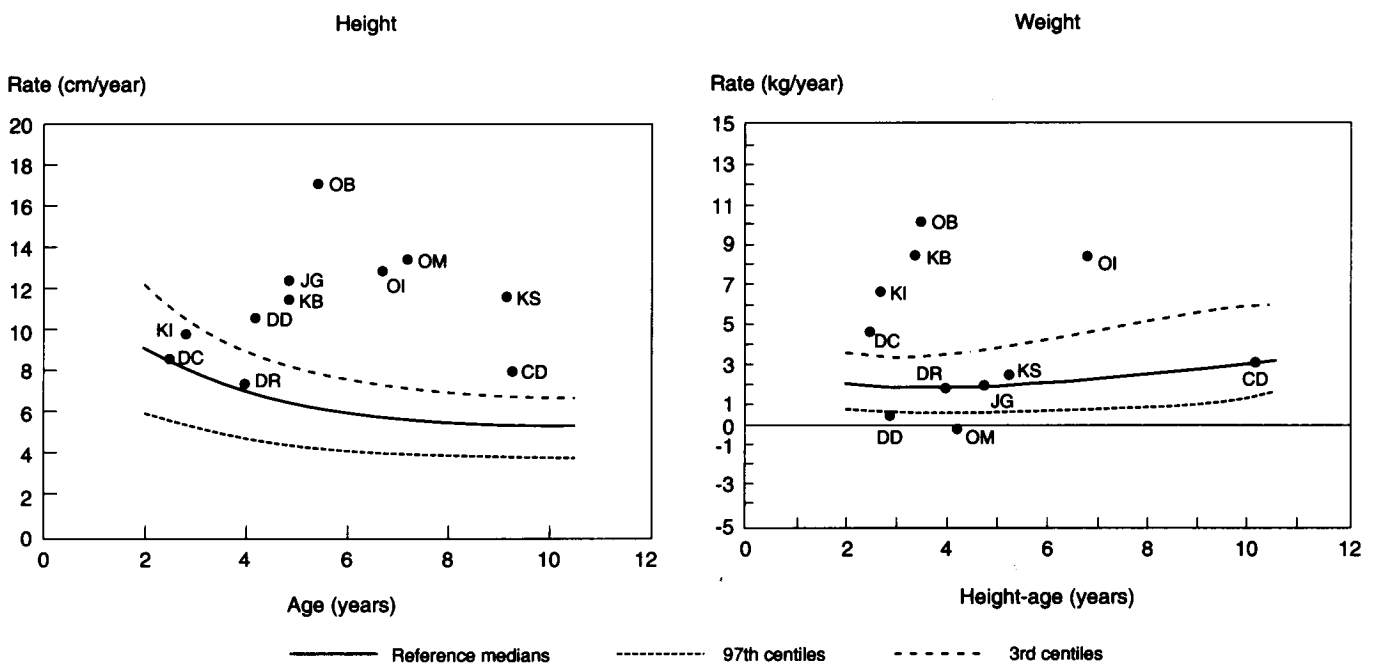
- *Diphyllobothrium.* Diarrhea occasionally occurs. In cases where the worm is situated high in the small bowel, vitamin B_{12} deficiency with a macrocytic anemia may be found.
- *Tenia saginata.* Passage of motile proglottids through the anus may be felt.
- *Tenia solium.* There are few symptoms from the adult form in the intestines. Larval cysticercosis can result in epilepsy, raised intracranial pressure, and psychotic change.
- *Echinococcus granulosus.* Large, space-occupying lesions may develop primarily in the liver, resulting in hepatomegaly, or in the lungs, leading to hemoptysis.

DISABILITY AND MALNUTRITION. Malnutrition may be an important accompaniment of the specific manifestations of parasitism by many of the helminths, particularly when there are multiple infections of relatively high intensity. The worms of the small bowel may impair digestion and absorption. Loss of nutrients may occur as a result of inflammation and toxic secretions, and the systemic consequences of infection such as fever may increase the catabolic rate. There may be a deficit of specific nutrients such as vitamins (B_{12}) and minerals (iron) as well as protein and calories. It must be remembered that children are also exposed to a wide variety of bacterial, viral, and protozoan infections. Thus, the status of the individual is the outcome of all these infectious and nutritional forces. If virtually all the chronic helminthic infections could be eliminated as significant pathogenic factors, child health in the developing world would show clear improvement. Available findings of the literature on the chronic medical consequences of helminthiases—disability, developmental retardation, and malnutrition—are summarized in table 7-4.

The conditions resulting in serious disability—onchocerciasis, lymphatic filariasis, schistosomiasis, and cysticercosis—tend to be geographically focal. Nonetheless these conditions are of massive importance to the individuals affected and to communities of high endemicity. Given the control technologies to be discussed later in this chapter, the benefit-cost calculus in focal regions is likely to prompt the conclusion that control efforts are of very high priority.

The two main nutritional consequences of helminthiases are growth faltering and anemia, although other micronutrient deficiencies have been noted. Stephenson (1987, pp. 9–10) traces three channels that lead from infection to growth faltering—anorexia, nutrient losses through malabsorption, and decreased nutrient use because of impaired liver and spleen function. Whatever the mechanisms, a large and growing literature now provides some documentation of substantial growth impairment from the geohelminths and schistosomiasis. Figure 7-1 provides a dramatic illustration of both the magnitude of growth faltering which can result from moderate infection (in this case with *Trichuris*) and of its reversibility

Figure 7-1. Growth Following Treatment for Trichuris Infection



Note: Values for each child are shown (initials are for individual children). The reference medians and 97th and 3rd centiles are from the Tanner-Whitehouse data (sexes combined). The ages are shown at the mid-point of the interval over which average velocity was measured. Use of height-age rather than chronologic age standardizes for that component of weight increment attributable to increasing stature. A comparison between the chronologic age and the height-age of each child indicates the extent of initial stunting.
Source: Cooper and others 1989.

after anthelmintic treatment. The initialed points in the figure show the growth velocities for children four to eight months after worm expulsion, in relation to growth velocity norms (solid line) and the ninety-seventh percentile (upper dotted line). These effects are indeed dramatic, given that the children were returned to their previous (unhealthy) environment.

In chapter 18 of this collection, Pinstrup-Andersen and others discuss in detail the general causes and consequences of growth faltering and protein-energy malnutrition (PEM). Two further points are, however, worth noting here. First, the functional consequences of PEM are substantial in many domains (for example, mortality risk and mental development), making the nutritional consequences of helminthic infection an important concern. Second, although the attributable risk for growth faltering cannot, with available data, be divided among insufficiency of nutrient intake, viral and bacterial infection, and helminthic infection, it does increasingly appear that a significant proportion of attributable risk results from helminthiases.

The other main nutritional concern is anemia, the main functional significance of which is discussed at length in chapter 19 of this collection. Anemia, too, results from highly prevalent helminths. Levin (1988) has shown that control of anemia through dietary measures or supplementation can have very high ratios of benefits to cost; similar or better results would obtain from helminth control strategies in communities in which helminthic infections are important cofactors for anemia. It should be noted, however, that control of helminths is not a substitute for iron supplementation, because hemoglobin levels improve much more rapidly if iron is provided with an anthelmintic.

FUNCTIONAL CONSEQUENCES OF HELMINTH INFECTIONS. There are two main functional consequences of economic significance—reduced efficiency of education in imparting the general intellectual skills that are of far-reaching significance for economic development, and reduced productivity of labor (and, to a lesser extent, land) (World Bank 1980). Hayashi (1980); Rosenfield, Galladay, and Davidson (1984); and Andreano and Helminiak (1988) provide valuable discussion of the mechanisms of these effects. In table 7-5 we summarize available findings. With respect to both productivity and schooling the literature is weak—not only in the number and scope of states, but also in the (probably) systematic way in which the studies undertaken and the sampling procedures that were used were likely to underestimate effects (Andreano and Helminiak 1988; Prescott 1989; for education, see Pollitt and others 1989). No solid studies of determinants of school attendance were found, although an early literature in Japanese on the effect of helminthiases on school attendance does exist (Morishita 1980). Stephenson (1987, p. 87) provides a bibliography of relevant literature from Africa. It is also likely that adverse effects of infection on learning have been biased downward by failure to sample those not in school.

The magnitude of the documented functional consequences of the helminthiases is substantial. But the available literature probably underestimates effects and certainly fails to consider a broad range of significant conditions and environments.

Table 7-5. Functional Consequences of Helminth Infections

	Productivity Loss		*Educational Impairment*	
Infection	*Labor*	*Land*	*Reduced school attendance*	*Impaired learning*
Nematodes				
Hookworm	Improved physical fitness after treatment	n.a.	Plausible effect	Definite effects, probably because of anemia
Ascaris	n.a.	n.a.	Plausible effect because of malnutrition	n.a.
Dracunculus	Substantial	n.a.	Elevated absenteeism and dropout rates reported among infected children	n.a.
Onchocerca	Important effects because of blindness	Important though often overstated effects	n.a.	n.a.
Trichuris	n.a.	n.a.	Plausible effect	Definite effects
Lymphatic filaria	Plausible effect	n.a.	n.a.	n.a.
Trematodes				
Schistosomes	Heavy infection clearly implicated	Retarded investment in land productivity because of concern for schistosomiasis and irrigation projects	n.a.	Probably important only in heavy infections

n.a. Not applicable.

Source: Andreano and Helminiak 1988; Edungbola and others 1988; El Karim and others 1980; Evans 1989; Ilegbodu and others 1986; Kvalsvig 1988; Pollitt 1989; Prescott 1989; Seim 1990; Stephenson and others 1990.

These functional consequences almost entirely are borne by the poor. What the available evidence does strongly suggest is that, as an investment in the improved productivity of the poor, control of helminthic infections has high priority.

Strategies for Control of Helminthic Infections

In this section we consider the range of practical techniques and strategies which are available for the control of helminthic infections, and we briefly examine their relative effectiveness and practicality (table 7-6). In a technical assessment of this type it is necessary to treat the procedures separately, although in practice a multidimensional strategy of control may be employed. Furthermore, it is inevitable that discussion of procedures will focus on practical interventions rather than their method of implementation; in practice the method of implementation, in particular its community acceptability, affordability, and sustainability, may prove more critical to success in controlling infection than the intervention employed. The relative merits and costs of different strategies of implementation are discussed later.

Vector Control

The control of the snails that are the intermediate hosts of schistosomes and other trematodes traditionally has contributed to overall control measures. Three main strategies have been employed: chemical (molluscicides), environmental (removal of snail habitats), and biological (the use of natural predators or competitors). Although the latter two methods have a significant contributory role in control, molluscicides have been the most extensively used in practical control programs. Recent developments (the availability of safe drugs, rising environmental concerns, and the escalating costs of the only commercially available chemical molluscicide) have, however, tended to reduce the emphasis on this form of control

Table 7-6. Primary Preventive Strategies for Helminth Infection

Parasite	*Immunization*	*Chemoprophylaxis*	*Hygiene*	*Vector control*	*Health education*
Nematodes					
Ascaris *Trichuris*	Inadequately studied	Albendaxole; ivermectin	Sanitation	n.a.	Personal hygiene; latrine building; geophagia
Hookworm *Strongyloides*	No immediate prospects	Albendazole; ivermectin	Sanitation	n.a.	Personal hygiene; latrine building; soil contact
Enterobius	Inadequately studied	Albendazole; ivermectin	Perianal washing; clean bed linen	n.a.	Personal hygiene; family treatment; family transmission
Dracunuculus	Inadequately studied	none	Clean drinking water	Filter drinking water	Water source; water contact
Onchocerca	No immediate prospects	Ivermectin	n.a.	Larvicide	Vector avoidance; early treatment
Wuchereria/Brugia	No immediate prospects	Ivermectin	Mosquito nets; repellents	Larvicide; kill adults; bed nets; environmental changes	Early treatment; environment modification
Trematodes					
Clonorchis, Fasciola *Fasciolopsis, Opisthorchis* *Pargonimus*	Inadequately studied	Praziquantel	Sanitation	Molluscicide; environmental changes	Food preparation; latrine building
Schistosomes	No immediate prospects	Praziquantel	Sanitation	Molluscicide; environmental changes	Latrine building; water contact; water source
Cestodes					
Tenia	Inadequately studied	Praziquantel	Sanitation; meat inspection	n.a.	Food preparation; latrine building; livestock management; personal hygiene
Echinococcus	Inadequately studied	Albendazole	Meat inspection	n.a.	Food preparation; dog and livestock management
Diphylobothrium	Inadequately studied	Praziquantel	n.a.	n.a.	Food preparation

n.a. Not applicable.
Source: Authors.

(Cook 1987). Still, there may be an increasing role for naturally occurring molluscicides, because they can be produced locally, are affordable, and typically are biodegradable (Lemma 1987).

Control of the other significant trematode infections of humans is now largely focused on treatment (Rim 1986), combined with improvements in sanitation. The countries in Asia have found that the control of intermediate host snails in natural habitats or in aquacultural enclosures is not practically feasible or culturally acceptable. Cultural resistance has also inhibited the dietary modification required to prevent transmission by way of the second intermediate hosts.

Control of the lymphatic filarial infections has also traditionally depended upon vector control, in this case through the use of insecticides and larvicides and, perhaps most sustainably, through the environmental reduction of breeding sites. The main drug in current use (diethylcarbamazine) has proved to be of limited effectiveness as a control tool (Sasa 1977), although it has some effect on low-level transmission of *Brugia malayi* (Partono, Purnomo and Soewarta 1979; Partono 1985). The introduction of ivermectin may dramatically change the choice of control approach.

The control of onchocerciasis has also been dominated by strategies based on vectors, although it now appears that control of morbidity may be possible through use of the newly assessed drug ivermectin. The Onchocerciasis Control Programme in the Volta River basin is the largest example of a vector-control program for a helminthic infection. This program was initiated in 1975 in an area of 654,000 square kilometers and because of reinvasion of vectors from surrounding regions was expanded in 1978 to include another 110,000 square kilometers. Control is based on aerial spraying of the larvicide temefos on a seven-day cycle, which is possible only because of the large size of the vector-breeding habitats. The program is scheduled to run for at least twenty years, because of the longevity of the adult parasite, and has already achieved some success in disease and infection reduction. There are great concerns, however, about the development of resistance to the larvicide. It is also unclear whether the expense involved would permit the application of this method in other endemic areas.

Assessments of the cost-effectiveness of the Onchocerciasis Control Programme have been undertaken—initially by Prost and Prescott (1984) and, subsequently, by Evans and Murray (1987), who modified the parameter estimates of Prost and Prescott. We would conclude from these studies that the vector-control strategy of dealing with onchocerciasis might cost in the range of $100 to $500 per year of healthy life gained, considering only gains from reduction in blindness and discounting future benefits at about 3 percent.

Dracunculiasis has also proved susceptible to local eradication by control of the vector. The simple and economic procedure of filtering drinking water through cloth to remove the crustacean intermediate host has proved to be a culturally acceptable and effective method of control in many endemic areas, and it is the method of choice for controlling this helminthiasis until enclosed water supplies are available. Provision of such water supplies, combined with health education, has been shown capable of eradicating the disease within three years (Edungbola and others 1988, Paul, Isley, and Ginsberg 1986). Assuming that the cost of providing safe water is about $8 per capita per annum, that infection prevalence is reduced from 30 percent to negligible, that individuals are 50 percent disabled while infected, and that communities would be prepared to pay half of the cost of water supplies if there were no Guinea worm, it is estimated that provision of water costs about $25 per healthy life-year gained. Obviously variation in costs and prevalence will very much affect this estimate, but, very clearly, intervention is likely to be highly cost-effective in a broad range of conditions.

Because of the relatively limited geographical scope of dracunculiasis and the high effectiveness combined with low cost of control measures, it (along with poliomyelitis) has been judged eradicable by the International Task Force for Disease Eradication. African ministers of health have set 1995 as the target date for eradication from that continent. Hopkins and Ruiz-Tiben (1990) review these goals and the activities now under way for attaining them.

Improving Hygienic Facilities and Behavior

It is self-evident that the sanitary disposal of feces will break the life cycle of many helminths and prevent transmission. It is also true that the safe disposal of human waste will provide a significant measure of protection from a wide range of other human pathogens. Feachem and others (1983a) reviewed eight major studies of community-wide sanitation improvement and in seven cases there was evidence of a reduction in enteric helminth transmission. This does not mean, however, that merely providing a dwelling with a latrine will result in improvements in the health status of the household. In communities where only some of the dwellings have sanitation facilities there is rarely any correlation between the enteric helminthic infection status of a particular household and the presence of a latrine (Otto and others 1931). In some cases households with latrines actually have higher rates of infection than those that do not (Feachem and others 1983b), particularly if the latrine is poorly maintained. Sanitation programs have to be community-wide if they are to achieve full benefit.

Community-wide sanitational improvement is not without its problems, however. A study in Indonesia showed that the provision of latrines made no difference to local levels of soil contamination with geohelminth eggs, because children persisted in promiscuous defecation (Ismid and Rukmono 1980). Reduction in environmental contamination demands not merely the provision of latrines but also their use (Feachem and others 1983b). In Iran, it is claimed that the provision of latrines actually increased the incidence of enteric helminthic infection, since it made human excreta more readily available as a fertilizer for domestic vegetable gardens (Arfaa 1986). Clearly the implementation of sanitation programs demands parallel programs of health education and particularly careful attention to sociocultural acceptability (Kilama 1989).

In addition to these sociological problems there may be significant practical difficulties. Rural-urban migration has resulted in the development of unsanitary slums and shanty towns around and within the cities of the developing world (Harpham and others 1987). In Malaysia, where 36 percent of the total population live in such impermanent settlements, it has been shown that slum-dwelling children have very high rates of enteric helminthic infection (Bundy and others 1988a) and that these rates are much higher than those recorded for children living in the rural areas from which the children came (Kan and others 1989). Provision of even low-cost sanitation for such slum areas is compromised by practical limitations on space, the absence of community organization, and sociolegal constraints on land tenure (Harpham and others 1987).

The beneficial effects of improvements in sanitation may take a considerable period to become apparent. Pawlowski (1984) cites the example of Lombardy in Italy, where the prevalence of trichuriasis in schoolchildren took twenty-five years to decline from 65 percent to 5 percent. A reduction in parasitic infection as a result of sanitational improvement alone is likely to take decades before a significant change is apparent.

Sanitation offers the advantage over other control measures of providing a long-term solution. It has the disadvantage of requiring a large initial capital investment—although the actual cost varies a great deal, depending on the system selected (Cairncross and Feachem 1983)—and a recurrent cost for maintenance.

Improvement in sanitation is a desirable goal and should be a component of enteric helminth control. Because of cost and sociocultural constraints, however, such improvement is likely to be slow and capital-intensive to implement, and it is likely to take decades before significant reductions in infection levels are achieved. Upgrading of sanitation may be best perceived, therefore, as a means of consolidating the more immediate benefits of chemotherapy and as a program best developed as one part of an integrated strategy.

Vaccination

No vaccines against the helminthic infections of humans are currently available. Vaccine development is, however, the goal of a considerable body of current research, particularly research into schistosomiasis, and it is therefore worthwhile, considering the potential benefits which might derive from the availability of an effective vaccine. It is relevant to note that a vaccine has been developed to protect dogs from hookworm (Miller 1978) and that modern molecular and immunological strategies may accelerate the availability of vaccines against human helminths.

The effect of vaccination is to increase the size of the immune and uninfected class in an endemic population. The aim of vaccination, in population terms, is to reduce the basic reproductive rate, R_o, of the parasite population below unity in value (Anderson 1982; Anderson and May 1982). To achieve this, the proportion p of the population which must be effectively immunized (assuming that immunized individuals do not contribute to transmission) at any one time is given by:

$$(1) \qquad p = 1 - (1/R_o)$$

The available evidence suggests, however, that the acquired protection is unlikely to be life-long, in which case the approximate criterion is:

$$(2) \qquad p = [1 - (1/R_o)]\, v^{-1},$$

where v is the period of vaccine-induced protection in years. This modification has important consequences. For example, if the vaccine provides life-long protection against a helminth such as hookworm or *Ascaris* (R_o approximately 3), the community could be protected by a single program of 67 percent vaccination in infancy. If protection lasts for only two years, then approximately 40 percent of the population would have to be vaccinated every year to achieve adequate community protection (Anderson and May 1985). Unfortunately it seems likely that such repetitive programs would be required, because the available evidence indicates that natural infection affords humans little protection against reinfection (Wakelin 1978; Bundy and others 1987).

These analyses suggest that a program to control human helminthiasis by vaccination would be logistically similar to a chemotherapeutic program in that both would require repeated intervention. The relative merits of the two strategies would therefore depend on the cost both of vaccines as compared with drugs and of delivery of vaccination as compared with delivery of treatment.

It is also relevant to note that vaccines which provide partial protection (that is, reduce the intensity of infection) may provide a significant measure of morbidity control when used against helminthic infections.

Chemotherapy

Advances in anthelmintic chemotherapy during the past twenty-five years have constituted the most important factor in the reformulation of strategies of disease control, in which emphasis is placed more on reduction and minimization of human morbidity and less on the concept of total eradication of infection (Davis 1986).

Some forty anthelmintics are available for use in human and veterinary medicine. Almost all of them originated from the classical screening mechanisms employed by industry. It is to be hoped that advances in biochemical, molecular, genetic, and parasitological technology will lead to a more rapid progression in "designer drugs" than has been the case to date.

For the treatment of helminthic infections in human beings, an impressive list of compounds exists. A recent review of selected drugs in frequent use against nematode infections at the community level included the benzimidazole carbamates, albendazole and mebendazole (with cyclobendazole or flubendazole as alternatives), levamisole, pyrantel, and the

traditional piperazine salts (Davis 1985). Recent evidence suggests that ivermectin, the well-known macrocyclic lactone microfilaricide used in large-scale chemotherapy of onchocerciasis, is promising in use against the human intestinal nematodes (Naquira and others 1989). In worldwide use, these drugs are effective, in varying degrees, against *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, *Trichuris trichiura*, *Strongyloides stercoralis*, and *Enterobius vermicularis*. Infection with multiple parasites is the general rule and thus anthelmintics possessing a broad spectrum of activity will invariably command a favored place in the strategy and tactics of chemotherapeutic control.

In infections other than those caused by the geohelminths, all of which are nematodes, praziquantel is the drug of choice in all forms of schistosomiasis, other snail-borne human trematode infections, and the common cestode infections, *Tenia solium*, *T. saginata*, *Diphyllobothrium latum*, and *Hymenolepis nana*. Ivermectin has some efficacy against the filarial nematodes, as well as several of the geohelminths, especially *Strongyloides*.

In any consideration of intervention programs against helminths it is essential to distinguish clearly between the meanings of the words "control" and "eradication." A control program is the implementation of specific measures to limit the incidence of an infection (Gemmell, Lawson, and Roberts 1986). It is taken for granted that any successes will produce, in parallel, a reduction in human morbidity and mortality from the conditions in question. In contrast, eradication implies the reduction of the incidence of a specific infection to the point of continued absence of transmission within a specific area through a time-limited campaign (Yekutiel 1980).

It is clear that for the immediate future and perhaps even for decades, emphasis in the control of intestinal helminthic infections in humans will be placed on the reduction of human morbidity and mortality implemented through population-based chemotherapy. Population-based chemotherapy is implemented in one of two main ways: through mass chemotherapy or through screening (often called selective) chemotherapy.

Mass chemotherapy is the treatment of a total population whether infected or not. Because it is rarely practicable to examine everyone in a population except in small or moderate-size villages or in school surveys, mass chemotherapy as a control tactic is usually applied after sampling procedures have revealed the levels of infection. Where prevalence or intensity of infection is high, or where there is clear evidence of associated morbidity or mortality, mass chemotherapy is a perfectly feasible tactic for morbidity control because the modern anthelmintic drugs are highly effective, their toxicity to humans is many orders of magnitude less than the compounds used even as recently as the 1950s and 1960s, and population acceptance is good. Furthermore, it may be wasteful of scarce and finite human, financial, and technical resources to continue sample examination programs when the epidemiological data indicate high prevalence and intensity of infection. This strategy is attractive to public health officials as the organization and implementation is easily managed by good planning.

Identifying which prevalence levels are sufficiently high to justify mass intervention is based on little more than intuition at present. Further broad-based research is urgently required to provide usable guidelines. One large question concerns the point at which the risks (apparently very small) associated with treating uninfected individuals exceed the benefits of treating those who are actually infected. Analogous considerations have been made in developing policy for vaccination strategies, where it is now generally held that the risks associated with vaccination are sufficiently low to justify vaccinating uninfected individuals even when the probability of infection is minimal. Similar analyses of anthelmintic risks and benefits may indicate that mass chemotherapy is appropriate and acceptable down to prevalence levels so low that intervention is unjustifiable on economic and health grounds.

The alternative strategy is screening chemotherapy: the treatment only of infected members of a population, where infection is demonstrated by standard diagnostic procedures (for example, Kato examination for geohelminths and enteric schistosomes; nucleopore filtration or hematuria for *S. hematobium*).

In certain situations, a combination of methods may constitute the most effective strategy: after mass chemotherapy has lowered prevalence and intensity rates, then screening chemotherapy could be used to treat those individuals exhibiting residual infection on follow-up examination. Such a strategy will, however, result in considerable additional cost (discussed later).

Chemoprophylaxis as a Primary Strategy

The terms "chemotherapy" and "chemoprophylaxis" refer to the resolution or prevention of disease and have no specific implications for infection. Drugs used in the prophylaxis of chronic, noninfectious disease (for example, antihypertensives) reduce the symptoms but do not solve the underlying problem. Chemoprophylaxis with chloroquine against chronic *Plasmodium vivax* infection also has the primary aim of avoiding disease, and only when so-called causal prophylactics such as primaquine are used is the infection removed. In an analogous manner, anthelmintic methods of reducing parasitic infection may be seen as aiming to avoid helminthic disease even though infection may persist.

Strategies of controlling parasitic infections within communities of people, as opposed to individual patients, have changed surprisingly little in the last sixty years. The control stratagems developed during the 1920s—principally as a result of the Rockefeller Foundation Hookworm Campaign (Cort 1922; Smillie 1924; Chandler 1925)—remain a dominant influence on the practical design of control programs.

In one sense this is a tribute to the earlier work. In another sense, however, it perhaps indicates a reluctance to apply new concepts, developed over the past few decades, to the practical problems of community-wide control. Considerable advances have been achieved in the development of safe and more

effective anthelmintics and in the development of a global infrastructure for health delivery, but these advances have had relatively little effect on the prevalence of helminthic infection. In the almost four decades since Dr. Norman Stoll (1947) estimated that there were more helminth infections than people, the situation remains almost unchanged (Walsh and Warren 1979).

This situation undoubtedly reflects a complex of logistic constraints, ranging from lack of resources to lack of political will. It also indicates, however, a lack of appreciation of how to apply our rapidly improving understanding of the treatment of individuals to the development of programs for the treatment of communities (Walsh and Warren 1979).

A community strategy clearly depends on a thorough and detailed understanding of the population dynamics of the parasites of humans and an understanding of how an intervention in one component of the complex life cycle of a parasite might influence the overall pattern of transmission (Anderson 1988). Such understanding depends on precise assessment of the biological determinants of observed infection patterns (Warren 1973) and the development of a rigorous theoretical framework to describe the complexity of the multidimensional processes involved (Anderson and May 1985). The last decade has seen considerable development in both these areas, largely because population-based field study and the mathematical description of population dynamics have developed as a synergistic partnership. This linkage is perhaps best exemplified by age-group targeting, a strategy which was developed as a theoretical concept from mathematical analyses (Anderson and May 1982, 1985; Anderson and Medley 1985) developed from precise field studies (Croll and others 1982; Bundy and others 1985; Elkins, Haswell-Elkins, and Anderson 1986) and translated into successful, large-scale community control programs (Bundy and others 1989; Cabrera and others 1989).

The application of population dynamics to parasite epidemiology has shifted the focus of chemotherapy from the individual to the community. The principal area of progress has been in estimating the control effort (in treatment frequency, effectiveness, and coverage) required to achieve a given reduction in transmission (Anderson 1989; Anderson, May, and Gupta 1989). This permits the identification of chemotherapeutic regimens which are optimal, in dose minimization, both temporally and quantitatively, for controlling a specified level of parasite endemicity. Such an approach cannot alone define the overall strategy—there remains a major requirement to set these options within a context of broader logistic issues, particularly economic—but it can provide the decisionmaker with a range of quantitative estimates upon which strategic choices can be based.

Pharmacology

Although consideration of the pharmacology of a drug is essential whenever treatment or prophylaxis is considered, it is especially important when two or even three drugs may be used simultaneously. In attempting to control a broad range of parasitic infections concurrently it may be necessary to administer two or three medications to the same individual. In this section we examine these issues and briefly summarize what is known about the structure and modes of action of three of the most important anthelmintics.

BENZIMIDAZOLES. The first benzimidazole introduced commercially was thiabendazole. It proved to be an effective larvicide, and thus was useful in *Trichuris*, *Trichinella*, and *Strongyloides* infections (Prichard 1970). For the latter infection, thiabendazole proved to be 75 percent effective. The benzimidazoles continue to enjoy worldwide application in veterinary parasitology.

Mebendazole (Vermox) has had wide acceptance in clinical chemotherapy, and of late, albendazole (ABZ, Zentel) appears to be emerging as a compound of choice for treating nematodes in humans. It is of interest to note that the alkyl sulfide side chain of albendazole ($-S-CH_2-CH_2-CH_3$) favors the chemical reactivity of this sulfide *in vitro*. Thus, rapid sulfoxidation can occur *in vivo*. It is thought that this metabolite is the active moiety of this anthelmintic. However, the introduction of a bulky aromatic sulfide, as in mebendazole, fenbendazole, or oxfendazole, decreases the rate by which the sulfur is oxidized, and the metabolites of these later drugs appear more slowly.

It is widely accepted that the mode of action of the benzimidazoles is selective interference with polymerization of worm tubulin (Borges and others 1975). The observed inhibition of glucose uptake or of enzyme excretion is believed to be a secondary consequence. This view is strengthened by the finding that classical tubulin disrupters (colchicine and podophyllotoxin) can also inhibit fumarate reductase, as well as uptake of glucose in benzimidazole-susceptible *Haemonchus contortus* worms.

Interference with orderly cell development is nicely illustrated in parasites through the inhibition of *in vitro* egg hatches. It is interesting to note that drug concentrations which inhibit tubulin polymerization by 50 percent are about the same as those which inhibit 50 percent egg hatches in susceptible nematodes. This relationship has proved to be fairly constant for all the benzimidazoles described above.

PRAZIQUANTEL. Praziquantel is a polycyclic, mostly saturated, flat, planar compound, generically classed as a piperazinone-isoquinoline. The compound is chemically unique, quite unlike any other anthelmintic.

The most important effects of PZQ on trematodes or cestodes are the following, as described mainly in studies of *S. mansoni* or *S. japonicum*. Within less than thirty seconds after exposure to 10^{-7} molar PZQ, worms begin to contract, apparently as a result of a sudden tegumental leakiness, allowing the ingress of calcium ions. The muscles of the worms go into tetanus, they lose control of sucker action, and from their position in the mesenteric veins are swept into the liver. At low concentrations ($<10^{-7}$ M) the resultant inflooding of calcium also

activates carbohydrate use through the second messenger-serotonin system.

Within minutes after exposure to PZQ, the surface of the worm, previously held in equilibrium, begins to undergo dramatic disintegration. This process has been called vacuolation, or "blebbing." The contraction of the worm is probably reversible and by itself might not be fatal to schistosomes. The tegumental damage, however, exposes heretofore inaccessible antigenic sites. These sites attract phagocytes and granulocytes, which release proteolytic enzymes and invade the worms. The worms are entrapped and encapsulated by fibroblasts and then totally destroyed. Whereas other antischistosomal drugs, such as hycanthone or oxamniquine, induce tegumental shredding and disruption, PZQ induces widespread surface changes within minutes and under conditions in which the host is not affected.

IVERMECTIN. Ivermectin (IVM) is a semisynthetic macrocyclic lactone which was first described about ten years ago (Albers-Schoenberg and others 1981). The basic substance is a fungal fermentation product derived from the coil-like actinomycete *Streptomyces avermitilis*, which was first isolated from a soil sample from a Japanese golf course. Ivermectin is derived from a chemical group of congeners, the avermectins (AVRs).

As potential bacteriocidal or antifungal agents, the avermectin compounds found no real chemotherapeutic application, but, in the early eighties (Mrozik and others 1982a), powerful anthelmintic properties were demonstrated. Many chemical alterations of the basic structure have been examined (Fisher and Mrozik 1989) in the course of pharmacological investigation of the AVR compounds, and IVM has been found to be the most active moiety against mammalian parasites.

Although IVM was initially believed to block the neurotransmitter gamma-aminobutyric acid (GABA) (Campbell and others 1983), a recent review (Turner and Schaeffer 1989) has postulated that in target organisms IVM may bind to specific high-affinity (of the order of 10^{-10} to 10^{-12}) sites. As the result of IVM binding, an increased permeability to chloride ions follows, and affected nerves are depolarized. The authors add that GABA-mediated chlorine channels may also react with IVM but at generally higher concentrations of the drug (about 10^{-7} M).

IVM can induce a variety of pharmacological responses which are influenced by many factors, such as variation in the GABA system (Soderlund, Adams, and Bloomquist 1987), drug penetration into membranes, and solubility in the test system. For instance, in *Ascaris suum*, IVM injection causes rapid paralysis, which is neither flaccid nor rigid (Kass and others 1980; Kass, Stretton, and Wang 1984). In the free-living nematode *Caenorhabditis elegans*, IVM induces rigid paralysis. Thus, specific worms react quite distinctly to this drug. In consequence, laboratory studies which employ traditional nerve-muscle preparations may not reliably describe what happens in those parasites which affect humans.

From field and laboratory studies it is known that IVM profoundly affects microfilariae, including those that are still developing in the female. The result is that normal larvation is halted, as dead or defective microfilariae accumulate in the uterus. The effect of the drug is quite stage-specific, involving early ("stretched") microfilariae in the distal uterus, and not the more mature coiled types (Albiez and others 1988; Lok, Harpaz, and Knight 1988). Peripheral migrating microfilariae, when observed in the anterior chamber of the human eye, showed "abnormal and reduced winding and coiling" (Sobaslay and others 1987). In patients that have been treated with the drug, progressively fewer microfilariae are recovered in skin snips. In one study, three days after therapy microfilariae were reduced to 14 percent of control numbers. Microfilariae that emerged from skin snips of treated patients, however, did not appear to be immobilized by IVM (Mossinger and others 1988).

The microfilaricidal effect of a single treatment is very persistent. A reduction of dermal microfilaria density both reduces skin pruritis and temporarily blocks transmission to the vector fly (Cupp and others 1989). Likewise, corneal and limbic invasion by microfilariae is decreased or halted. Dadzie and others (1987), Newland and others (1988), and Taylor and others (1989) all reported that annual treatment was very helpful for patients with light to severe onchocercal eye disease.

The disadvantage of IVM is that single-dose therapy regimens do not destroy adult filarial worms. Female *Onchocerca volvulus* (Greene, Brown, and Taylor 1989), *Loa*, and the oligo-pathologic agent *Mansonella perstans* (Richard-Lenoble and others 1988) as well as *Wuchereria bancrofti* (Kumaraswami and others 1988) all resume larvation within months after exposure to IVM. In the species mentioned above, the drug causes significant and long-term reduction in circulating microfilariae. Therefore, most recent reviews conclude that IVM is superior to, and safer to use than, diethylcarbamazine, a drug which has been used for half a century in the treatment of filariasis (Albiez and others 1988; Kumaraswami and others 1988; Ottesen and others 1990). Whether the combination of IVM with a benzimidazole (such as albendazole) will increase the filaricidal potential remains as yet undetermined.

Activity of IVM against intestinal nematodes is striking. According to recent field reports (Nalin and others 1987; Naquira and others 1989) a single or double dose of IVM will remove 100 percent of *Ascaris lumbricoides*, and 70 to 85 percent of *Strongyloides stercoralis*, *Enterobius vermicularis*, and *Trichuris trichiura*. Patients with hookworms achieved some benefit, since egg production was decreased by approximately 60 percent. A dosage of 200 micrograms per kilogram of IVM, however, resulted in only about 20 percent long-term cure at three months.

DRUG METABOLISM AND TOXICITY. Albendazole is poorly absorbed (less than 5 percent) by the gastrointestinal tract, which is appropriate because most nematodes that ABZ removes are enteric. Of the fraction of ABZ that is absorbed, essentially 100 percent is metabolized in the liver, yielding an albendazole sulfoxide. This metabolite may be the active moiety of the drug. The parent compound, ABZ, cannot be detected in the

serum. The peak concentration is reached in about 2 hours, and the plasma half-life is about 8.5 hours. Hydroxylation and hydrolysis products of albendazole-sulfoxide have been found in the urine.

Praziquantel is extensively metabolized after oral administration, apparently in first-pass liver oxidation. Most (60 to 80 percent) of the hydroxylated PZQ products are excreted in the urine, as well as a small residue by way of the bile and feces. It has a very short half-life of 1 to 1.5 hours.

Ivermectin, when its pharmacokinetics were followed in humans, showed a rather complex excretion pattern. Its half-life, and that of the metabolites, is about 12 hours, and includes an enterohepatic recycling pathway. Only 1 percent of the metabolites are found in the urine; most of the excretion is by way of the bile. The degradation products may be fatty-acid ester conjugates, as well as the aglycon, that is, the basic structure stripped of the two oleandroses. Some IVM may be stored in body fat, and released slowly; this might explain why microfilaricide activity persists for months after medication.

In general these three drugs are not toxic to humans when administered as single-dosage agents. Those side effects which have been cataloged are restricted to what one might consider to be "mild" reactions. They tend to be symptoms of vertigo, nausea, or other gastrointestinal distress, evanescent skin pruritis, and orthostatic hypotension. Although such reactions are disturbing, they are not life-threatening.

Although the toxicity and side effects of the new broad-spectrum anthelmintics are rare enough and mild enough for their use in mass chemoprophylaxis, it is likely that these untoward reactions can be substantially reduced without compromising the goal of disease control. Recommended drug dosages are usually a compromise between the highest cure rates possible and the maximal acceptable level of side effects. Because cure, or as the pharmacologists put it, a 100 percent lethal dosage, is unnecessary in the context of helminth disease control, it is theoretically possible to reduce markedly the drug dosages and their attendant side effects while also decreasing intensity of infection below disease-producing levels.

Several dosage-ranging studies have been performed with antischistosomal drugs. Investigators in Saint Lucia (Cook, Jordan, and Armitage 1976) and Kenya (Warren and others 1978) examined the effects on prevalence, the intensity, and the side effects of a relatively toxic intramuscular drug, hycanthone, in patients with *S. mansoni* infections. In Saint Lucia it was observed that a reduction of the recommended dosage (3 milligrams per kilogram of body weight) to half that amount (1.5 milligrams per kilogram) reduced vomiting from 51 percent to 3 percent. In Kenya there was no vomiting at dosages of 1.5 milligrams per kilogram of body weight or lower. The total egg output was reduced by approximately 98 percent with both dosages in Saint Lucia and 96 percent with the lower dosage in Kenya. In the Saint Lucia study reductions in hepatomegaly and splenomegaly were similar at both dosages. Recently, Polderman, Gryseels, and DeCaluwe (1988), in studies of schistosomiasis mansoni in Zaire, found no difference in cure rate or egg output with dosages of praziquantel of 40 and 30 milligrams per kilogram of body weight. King and others (1989), studying the treatment in Kenya of schistosomiasis hematobia with praziquantel at 40, 30 and 20 milligrams per kilogram showed a difference in cure rate ranging from 85 to 58 percent but no significant difference in reduction of egg counts (which ranged from 99.6 to 97.6 percent) and no difference in the marked decrease in morbidity as evinced by hematuria and proteinuria. Taylor, Murure, and Manomano (1988) in Zimbabwe showed similar results with praziquantel for both *S. mansoni* and *S. hematobium*. It should be noted that the original dosage recommended for albendazole was 200 milligrams per kilogram of body weight, or half the amount presently in use.

POTENTIAL USE OF THESE DRUGS IN MASS CHEMOTHERAPY. Because a substantial proportion of infections may involve more than one parasite species, there is often a need to treat the infection concomitantly with albendazole, ivermectin, and praziquantel. This raises the question of the effectiveness and safety of multiple treatment, particularly if it forms part of a community program. Note that these concerns are least severe for concomitant therapy that makes use of existing well-characterized anthelmintics. Combination of the anthelmintics into a single tablet, which might offer advantages in the logistics of delivery, would represent a new formulation and require extensive reassessment of toxicity.

A crucial aspect of the problem of anthelmintic therapy with multiple drugs is the issue of cross-interference or cross-reactivity. Because these agents have not been administered simultaneously to patients under controlled conditions, one can only speculate about the result. Fortunately, it seems that each of these three drugs acts at different biochemical points which do not overlap.

Therefore, an optimistic view is that these three broad-spectrum anthelmintics will be found to be mutually chemotolerant. Extensive clinical experience reveals limited toxicity and predominantly mild side effects for each of these compounds. When these drugs are taken together, will the side effects increase? Pilot trials are urgently needed before mass campaigns requiring two or three of the drugs are undertaken. In many areas, however, only one or two drugs will be necessary.

THE PROBLEM OF INDUCTION OF DRUG RESISTANCE. It has been suggested that in treatment of helminths one need not be concerned about the induction of drug resistance. In bacterial infections, the organisms have a short life span and a rapid rate of multiplication within the host. Thus, if bacteria are exposed to antibiotic drugs, they frequently undergo genetic selection which allows succeeding generations to circumvent the metabolic lesions caused by the antibiotics. When less-than-optimal concentrations of drugs are administered, succeeding generations with increasingly greater resistance are selected.

It has been asserted that this is less probable with most helminths, which have a much longer residence time in hu-

mans, and which, in any case, do not multiply within the host. But is the conclusion, that worms are unlikely to develop resistance, justified? Experience with both benzimidazoles and with ivermectin suggests that although the initial (P1) generation might be highly susceptible, succeeding generations (F1 through F20) can become less sensitive or altogether refractory to these drugs (Behm and Bryant 1985).

The phenomenon of resistance to the benzimidazoles has been most carefully studied in the veterinary field. Numerous strongyloid worms of domestic livestock have been found to be resistant to a spectrum of benzimidazoles (Lacey 1986). In fact, the development of resistance to thiabendazole was the basic reason for the introduction of other members of the benzimidazole series.

In assessing long-term effectiveness of IVM, Egerton, Suhayda, and Eary (1988) have reported decreasing sensitivity of *Haemonchus contortus* to the drug after only four generations of worms were exposed to drug concentrations designed to eliminate 95 percent of the parasites. By the seventh generation, a substantial increase of IVM was required to continue elimination of 95 percent of the worms. The induced resistance appeared to be stable through many generations.

Clearly, there are reasons to think that development of resistance to the drugs contemplated for mass chemotherapy will eventually occur. The onset of resistance is related to the dosage used for each treatment: adequate drug amounts with high killing indexes delay the onset of resistance.

In making a decision on the dosage recommended for a field campaign, answers to the following questions must be addressed:

- How important is it to treat patients under conditions in which side effects are either absent or extremely tolerable?
- How necessary is it to reduce the total amount of medication in order to control the cost of mass chemotherapy?
- How tolerable might it be to reduce the worm burden, while leaving a few viable (and egg-producing) worms behind? Could the surviving worms eventually produce a strain of offspring which are resistant to the chosen medication?

On an optimistic note, one may find that the combination of albendazole and ivermectin is particularly desirable in the sense that these two anthelmintics may potentiate each other. The combined use of levamisole and a benzimidazole against veterinary nematodes has an established history in veterinary practice. There is also evidence that mebendazole is useful in the treatment of onchocerciasis in cattle. Thus, combining ABZ and IVM might significantly reinforce a weak action of the latter on filaria, as well as on hookworms.

The Potential for a Multiple-Species Strategy

The traditional approach to developing a parasite control program has been to plan a specific strategy focused on a single parasite species. Although this has the advantage of simplicity, it ignores the reality that parasites have broadly overlapping geographical distributions and that multiple infection in the same individual is much more common than single infection. It also ignores the practical reality that a drug delivery system developed for one anthelmintic can readily deliver others (or even other agents such as vitamin A) for little additional cost. In this section we collate secondary data on the global distribution of geohelminthic, schistosomal, and filarial nematode infections in an attempt to identify which combinations occur most commonly in which geographical areas. The focus is on developing countries, and the analyses exclude North America, Europe, anglophone Australasia, and the former U.S.S.R.

The geographical distributions described in table 7-2 inevitably result in considerable areas of overlap. Because of the ubiquity of the geohelminthiases these can be perceived, to a large extent, as a broad background of geohelminthic infection on which are imposed areas of additional infection with the schistosomes, the filarial nematodes, and other helminths. This results in a complex distribution of multiple infections, involving three species of geohelminth, four species of schistosome, and three species of filarial nematode in more than fifteen different combinations.

Developing a chemotherapeutic intervention strategy for this complex of multiple infections, however, is considerably simplified by the availability of broad-spectrum anthelmintics. Single drugs are now available for treating all the most important geohelminthic infections (albendazole or mebendazole), all the schistosomes, all the significant digeneans, and all the main cestodes (praziquantel); and recent studies suggest that ivermectin is effective against the primary filarial nematode infections and *Strongyloides*.

The broad spectrum of activity of the available anthelmintics reduces to five the number of drug regimens required to treat the whole complex of multiple infections. In terms of global area, the largest requirements are for albendazole alone (in Central and South America, North Africa, and South Asia), or with praziquantel and ivermectin (in the north and east of South America, most of Sub-Saharan Africa, and in Southeast Asia). This is also the situation in terms of population density, as can be seen in table 7-7, although the relative importance of the parasites (and hence the drug regimens) varies regionally: in Central and South America, geohelminthiasis alone is the dominant infection except in Brazil; in Africa, geohelminthiasis is typically combined with both filariasis and schistosomiasis; and in Asia, no one combination is dominant. Table 7-7, however, does not take into consideration other predominantly Asian trematode infections such as *Opisthorchis*, *Clonorchis*, *Fasciolopsis*, and *Paragonimus*.

Further analyses of these data allow some estimates to be made of the proportion of the population requiring a particular anthelmintic. Table 7-8 indicates that the requirement for a drug against geohelminthiases is likely to be twice as great as for those against schistosomiasis or filariasis. This is a natural consequence of the ubiquity of geohelminthic infection; many

Table 7-7. Estimated Total Population in Areas Endemic for Various Combinations of Helminthiases
(millions)

Predominant helminthiasis	Central and South America	Africa	Asia	Total
Geohelminthiasis	210	128	801	1,139
Geohelminthiasis and filariasis	53	205	500	758
Geohelminthiasis, filariasis, and schistosomiasis	99	296	755	1,150
Geohelminthiasis and schistosomiasis	28	133	311	472
Schistosomiasis	0	44	0	44

Note: Total population does not necessarily reflect number of people infected or at known risk.
Source: Authors.

of those requiring treatment for gastrointestinal nematodes are likely to have concurrent infection with schistosomes or filarial nematodes, but not vice versa.

It should be stressed that these are crude estimates based on the total population of the endemic area and do not represent the population infected or the population at a known level of risk (calculation of these statistics was beyond the scope of the present study). The actual quantities of anthelmintics required will depend on data on the prevalence and intensity of the various infections in a particular area.

These studies suggest that control of multispecies helminthic infection will require specific combinations of anthelmintics. In the following section we consider how an understanding of the population dynamics of these infections can provide guidelines for developing control strategy.

Frequency of Treatment, Coverage, and Dosage

In the development of community-based programs for the control of helminthic infections, a sound understanding of epidemiological patterns forms a template for the use of scientific methods to calculate the intensity and frequency of anthelmintic treatment required to block transmission (community-wide) or to prevent morbidity (Anderson and May 1985). Ideally, a variety of types of information is required to assess epidemiological patterns and processes: age-stratified profiles of prevalence and intensity of infection; the distribution of worm loads per person within an age class; and longitudinal (that is, through time) changes in intensity and prevalence following anthelmintic treatment (rates of reinfection). For the main helminths of humans, such information is available (although variable in quality) for many regions in developing countries. In this section we summarize the central features of the dynamics of helminth populations as they concern the control of helminthic infection.

Table 7-8. Requirement for Anthelmintics Based on Proportion of Population Living in Areas Endemic for Various Combinations of Helminthiasis
(percentage)

Anthelmintic	Central and South America	Africa	Asia
Albendazole	58	44	50
Praziquantel	23	29	27
Ivermectin	19	27	23

Source: Authors.

Helminths are invariably aggregated in their distribution within human communities (or age or sex groups) such that most people harbor few worms and a few harbor many. It is typically the case, irrespective of helminth species, that more than 70 percent of the total population of worms are harbored by less than 30 percent of the human community. In addition, wormy people (who are more likely to show clinical symptoms and who are the primary contributors to morbidity statistics) are more frequently children than adults (Bundy and others 1988c).

Many recent studies of reinfection in individual patients following anthelmintic treatment show that those heavily infected prior to treatment tend, on average, to acquire heavy infection following a period of reinfection. Predisposition to heavy or light infection has been demonstrated for many geohelminth, schistosome, and filarial nematode species. The underlying mechanisms that generate predisposition are poorly understood at present, but some combination of behavioral, social, nutritional, and genetic factors is the likely cause.

In many rural and urban communities in developing countries, where social and economic conditions have changed little in many decades, changes in the prevalence and intensity of infection with age reflect changes through time. In other words, the rate of acquisition of infection (or exposure) as individuals age reflects the intensity of transmission in a defined area: the greater the transmission, the more rapidly infection prevalence and intensity rises with age. For helminthic infections, the intensity (usually measured indirectly by fecal egg counts) is a better reflection of this rate of transmission. Because of the highly aggregated distributions of worm numbers per person, large changes in mean worm burden may be accompanied by small changes in prevalence (Anderson 1982). As such, intensity is a much more sensitive indicator of both the rate of transmission and the effect of any given control program.

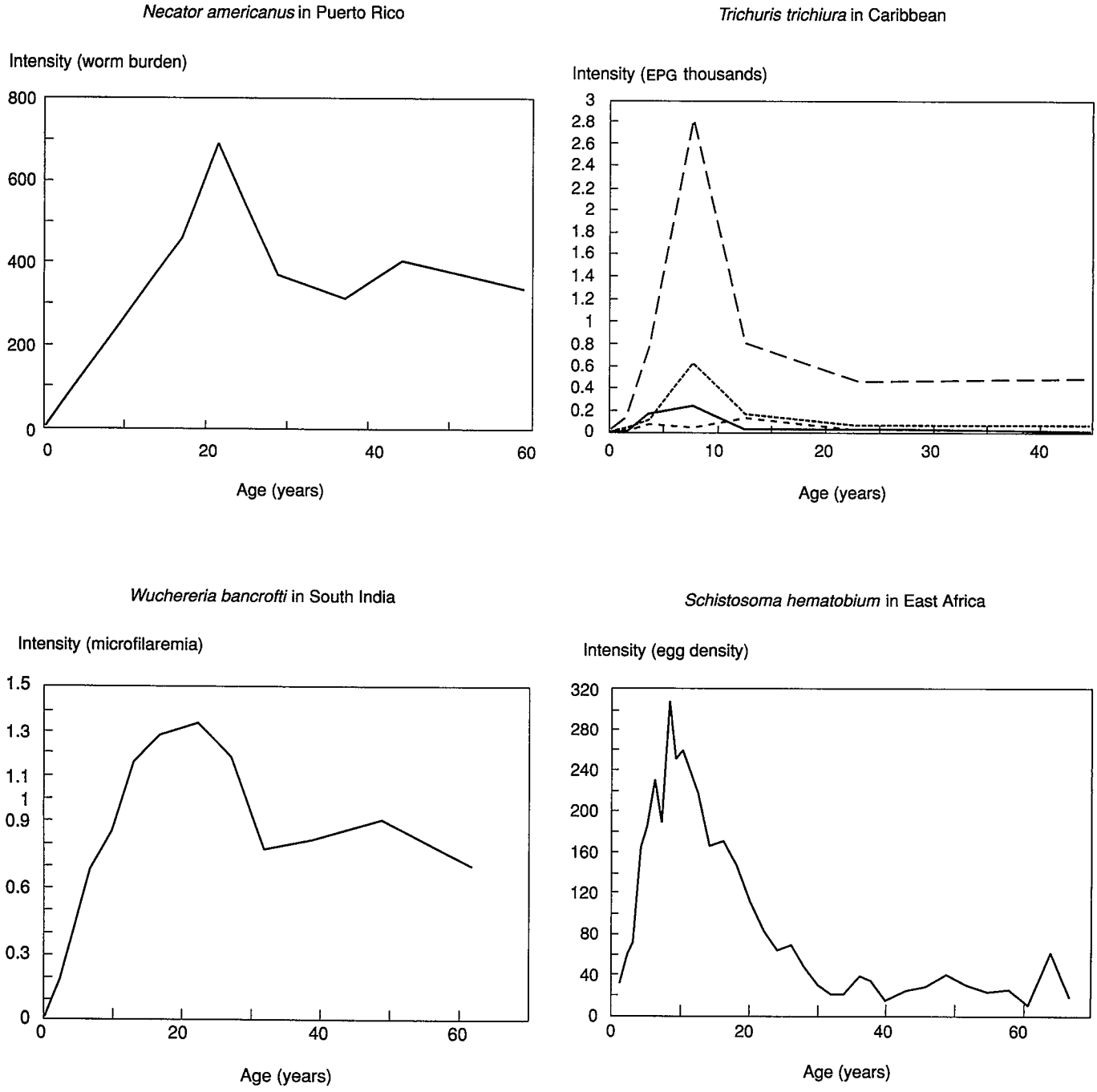
Typical age-intensity patterns for helminths in human communities are convex in form. Intensity usually rises from zero at birth to a peak in child, teenage, or adult age classes, depending on the intensity of transmission. In the case of some filarial infections, and perhaps hookworm, the intensity tends to plateau, without exhibiting a convex hump. Convex patterns with age may reflect age-dependent changes in exposure to infection or the slow build up of acquired resistance. In practice both are probably important, because behavioral studies of the acquisition of schistosomes and geohelminths point to the importance of behavior (Bundy and Blumenthal 1989), whereas the observation that increasing degrees of convexity in the age-intensity profile correlate positively with the inten-

sity of transmission suggests a role for acquired immunity (Anderson 1987). Some typical profiles for various species of helminths are recorded in figure 7-2.

Following anthelmintic treatment, people in areas in which transmission is not interrupted reacquire worms at a rate dependent on the net force or intensity of transmission. The rate of reacquisition depends on the species of helminth (and its biological and life-cycle characteristics) as well as the intensity of transmission within a given community. In table 7-9 we summarize typical return times to preinfection intensities of infection in areas of endemic infection with moderate to intense levels of transmission.

The implication of this trend for reinfection is that chemotherapy must be applied repeatedly to ensure low levels of infection and hence morbidity. If treatment is frequent enough, then transmission can in principle be blocked and the parasite

Figure 7-2. Age Intensity Profiles for Common Helminthiases



Source: (Left to right, top to bottom) Hill 1926; Bundy 1986; Rajagopalan and others 1989; Bradley and McCullough 1974.

Table 7-9. Time to Return to Pretreatment Levels of Infection after Anthelmintic Therapy, in Areas of Moderate to Intense Transmission, and the Life Expectancy in the Human Host
(years)

Parasite	*Return time*	*Life expectancy*
Trichuris trichiura	<1	<1
Enterobius vermicularis	1	<1
Ascaris lumbricoides	<1	1
Ancylostoma duodenale	2–3	2–3
Necator americanus	2–3	2–3
Schistosoma mansoni	3–5	3–5
Schistosoma hematobium	3–5	3–5
Schistosoma japonicum	3–5	3–5
Onchocerca volvulus	>5	>8
Wuchereria bancrofti	>5	>5

Source: Authors.

eradicated. In practice, however, spatial factors often result in reinvasion from neighboring areas where control effort is less effective.

Return times to pretreatment infection levels are inversely correlated with the life expectancy of the parasite in the human host (Anderson 1986; Anderson and May 1985; Bundy and others 1988b). If life expectancy is short, the return time is fast, and *vice versa.* Current estimates (often very crude and approximate) of the life expectancy of some important human helminths are given in table 7-9.

The intrinsic properties of a parasite to reproduce and transmit from host to host may be measured by reference to its basic reproductive rate, R_0. This quantity defines the average number of female worms (for a diecious species) produced by one female throughout her reproductive life span that themselves gain entry to a host and survive to reproductive maturity in a susceptible human population. Clearly if R_0 is less than one the parasite will not persist endemically in the human community. This constraint sets the target for control programs—the intensity of control (whether by chemotherapy or other methods) should aim to reduce reproductive success to less than unity in value (on average). If R_0 is greater than one the parasite will persist. The magnitude of R_0 for a given parasite in a defined human community can be crudely measured by reference to the rapidity with which the average intensity of infection rises in infants and children as they age. The faster the rise, the higher the value of R_0 for that parasitic species, in a given situation. Some rough estimates of R_0 for various parasites in various settings are listed in table 7-10.

Table 7-10. Estimated Basic Reproductive Rate (R_0)

Parasite	R_0	*Location*	*Source*
Ascaris lumbricoides	4–5	Iran	Croll and others 1982
Necator americanus	2–3	India	Anderson 1980
Trichuris trichiura	4–6	St. Lucia	Bundy and Cooper 1989
Schistosoma mansoni	1–2	Egypt	Hairston 1965
Schistosoma hematobium	2–3	Egypt	Hairston 1965
Schistosoma japonicum	1–4	Philippines	Barbour 1982
Onchocerca volvulus	>9	Côte d'Ivoire	Dietz 1982

Source: See last column.

To block transmission of any given parasite effectively, the frequency of treatment required will depend not only on the ecological characteristics of the species (for example, life expectancy) but also on the intensity of transmission in that endemic locality (the magnitude of R_0). In order to generalize about the frequency of treatment it is necessary to assume a standard pattern for the transmission of a set of parasites (the species composition in a defined area or region). In what follows we assume that, prior to control, transmission was at moderate to intense levels.

Recent analytical work on the transmission dynamics of helminth parasites in human communities has led to the derivation of a "control criterion" of a fairly general character, which defines the frequency (in units of time) and the coverage (the proportion of the community treated during each intervention cycle) of treatment ideally required to reduce transmission, community-wide, to very low or negligible levels. This level of control should be significantly greater than that required to reduce morbidity. For an anthelmintic drug of effectiveness h, whose effectiveness defines the proportion of an individual's worm load killed by a single or a short course of treatment (for most drugs $h > 0.9$), the proportion of a human community, p, that must be treated per unit of time (for example, year or month) to block transmission is given approximately by the relationship

$$(3) \qquad p > \{1 - \exp[(1 - R_0)/L]\} / h$$

Here R_0 is the basic reproductive rate and L is parasite life expectancy in the human host (Anderson 1986). If effectiveness is less than 100 percent (that is, $h < 1$) and R_0 large, then it is possible that the value of p will be greater than one. In these cases the units of the life expectancy term, L, must be reduced (that is, years to months) such that the proportion to be treated is calculated on a more frequent cycle (shorter time interval).

In general, if we use the values of R_0 and L listed in table 7-11, for a drug that is 95 percent effective ($h = 0.95$) we can provide some rough guidelines on the coverage and frequency of treatment for the main helminths in areas of moderate to high transmission intensity. These guidelines are summarized in table 7-11.

In assessing the information presented in this table it must be noted that the parameter estimates (of R_0 and L) are rather crude at present. As a consequence of this, the estimates of frequency and coverage are very approximate and should only be viewed as rough guidelines.

The data in table 7-11 indicate that when considering single (or short course) treatment for multiple infections the interval between treatments will depend on the precise mix of parasite

Table 7-11. Estimated Ideal Coverage and Frequency of Drug Treatment to Reduce Parasite Transmission to Very Low Levels

Parasite	R_0[a]	L (years)[b]	Coverage (percent)	Frequency of treatment (years)
Trichuris trichiura	5	1	80–90	0.5–1
Ascaris lumbricoides	5	1	80–90	0.5–1
Necator americanus	2.5	2.5	70–80	2
Ancylostoma duodenale	2.5	2.5	70–80	2
Schistosoma mansoni	2	4	70–80	4
Schistosoma hematobium	2	4	70–80	4
Onchocerca volvulus	10	8	70–80	1
Wuchereria bancrofti	10	8	70–80	1

a. Basic reproductive rate.
b. Parasite life-expectancy.
Source: Authors.

species. In areas where filarial worms or geohelminths predominate, an ideal frequency is every year. For geohelminths, this interval might be slightly lengthened if treatment is targeted at schoolchildren, since this age group tends to be heavily infected. For hookworms the ideal interval is two years, whereas for schistosomes it is roughly four years.

These theoretical intervals are longer than those that are commonly applied in practice. There are two main reasons for this. First, current estimates of frequency are often based on time taken for prevalence, rather than intensity, to rebound to pretreatment levels. Because intensity is more closely correlated with transmission (and morbidity), it is the slow rebound in intensity which should more appropriately determine the frequency of treatment. Second, current estimates of the frequency of intervention are usually based on the rate of reinfection observed after the treatment of a few individuals living in an area of otherwise uncontrolled transmission. Reinfection rates under these conditions will be much higher than if the population were treated as part of a community-wide control program, thus giving a misleading impression of the frequency of treatment required. Examples of situations under which community-wide treatment results in slow rates of reinfection with schistosomiasis are described by Wilkins (1989).

In all cases, the coverage of treatment should be high: typically, 70 to 90 percent of the target community. In areas of high-intensity transmission, the intervals between treatments should be shorter and the population coverage greater, whereas in areas of low transmission, lower frequencies and coverage would be appropriate.

These preliminary analyses suggest two important conclusions of relevance to the development of a strategy of helminth control. First, they indicate that recent advances in anthelmintic development have made multispecies control of the main helminthiases a plausible option. Theoretically, the broad spectra of modern anthelmintics should permit the treatment of a complex range of infections using only five combinations of three anthelmintics. More precise estimation of the logistic implications of this strategy—in particular, finely stratified data on the global prevalence and intensity of infection—should be possible from existing data sources, but further studies are necessary to determine the effectiveness and pharmacodynamic properties of these drugs when used concomitantly.

Second, the analyses suggest that recent advances in the theory of population dynamics permit the estimation of "optimal" chemotherapeutic interventions (in frequency and coverage of treatment) for a given parasite species in a given locality. These estimates currently lack precision because of the absence of adequate data, but they may serve as broad guidelines for the development of control strategy. Further work is required to improve procedures for parameter estimation (particularly R_0), and to collect appropriate data for the range of parasite species in different epidemiological situations. These conclusions suggest that the study of parasite population dynamics and epidemiology has an important, and increasing, role to play in the development of policies of parasite control.

Cost and Effectiveness of Screening and Targeting

Many options are available for the delivery of chemotherapy to the community. Both economic and epidemiological factors determine which is the most cost-effective method in a given situation (Prescott 1987; Prescott and Bundy 1989: Prescott and Jancloes 1984). At the broadest level, there is an obvious choice between the treatment of children only (targeted chemotherapy) and the treatment of the whole population, including adults (population chemotherapy). For each of these options there is a choice between the treatment of all individuals, irrespective of infection status (mass chemotherapy), and the treatment of individuals shown to be infected after diagnostic testing (screening chemotherapy). In the latter case, treatment can be given to all infected persons (prevalence screening) or only to those individuals with "heavy" infections (intensity screening) (terminology adapted from WHO 1985). Each of these six different options (table 7-12) is associated with different costs and different levels of effectiveness, defined as reduction in prevalence, intensity, morbidity, or some other variable. Effectiveness should ideally also be defined per unit of time: because reinfection invariably occurs after treatment, the effective reduction in prevalence, intensity, and morbidity can be defined only for a particular observation or intervention period.

In this section we present an analysis of the cost-effectiveness of the alternatives outlined above in a standard population with defined epidemiological, economic, and behavioral parameters. The analyses are essentially static because, at this stage, they do not reflect parasite population responses to the various interventions. The more complex problem of dynamic economic analysis, taking account of differing reinfection patterns, is a subject for future research.

Table 7-12. Chemotherapeutic Strategies for Control of Helminthiasis

Targeted population	No screening		Screening for infection		Screening for intensity of infection	
	Population treated	Control strategy	Population treated	Control strategy	Population treated	Control strategy
None	All children and adults	Population mass (PM)	All infected children and adults	Population screening for prevalence (PSP)	All heavily infected children and adults	Population screening for intensity (PSI)
Children	All children	Targeted mass (TM)	All infected children	Targeted screening for prevalence (TSP)	All heavily infected children	Targeted screening intensity (TSI)

Source: Authors.

THE BASE CASE. Using representative data, we have simulated the costs and effectiveness of the chemotherapy options for a standardized population in the scenario for the base case shown in figure 7-3. The simulations model a chemotherapy program implemented for two years with six-month treatment cycles. Total costs per capita for the entire two-year program are estimated from unit cost data derived from an actual control program (Bundy and others 1989; Terry, Bundy, and Horton 1989). Because costs vary between countries, these data should be interpreted as comparative rather than absolute. Note that per capita costs refer to the cost of the entire program (two years) per person in the population (N = 1 million) whether or not infected. Effectiveness is measured by the proportion of total heavy infections (adults plus children) treated, assuming the epidemiological and behavioral parameter values summarized in table 7-13.

In considering effectiveness only, without regard to budget constraints, the main result in the base case is that the mass chemotherapy strategies are much more effective than any of the screening options. Population mass chemotherapy emerges as the best option, treating 94 percent of heavily infected cases, compared with 80 percent for targeted mass chemotherapy. By contrast the screening options are only about 60 percent effective. This result reflects the importance of compliance behavior: the effectiveness of mass interventions is modified only by compliance with treatment, whereas the effectiveness of screening-based interventions is also modified by compliance with the diagnostic screening test. Because screening compliance rates are typically much lower than treatment compliance, especially for adults, any screening approach must inevitably treat fewer infected individuals.

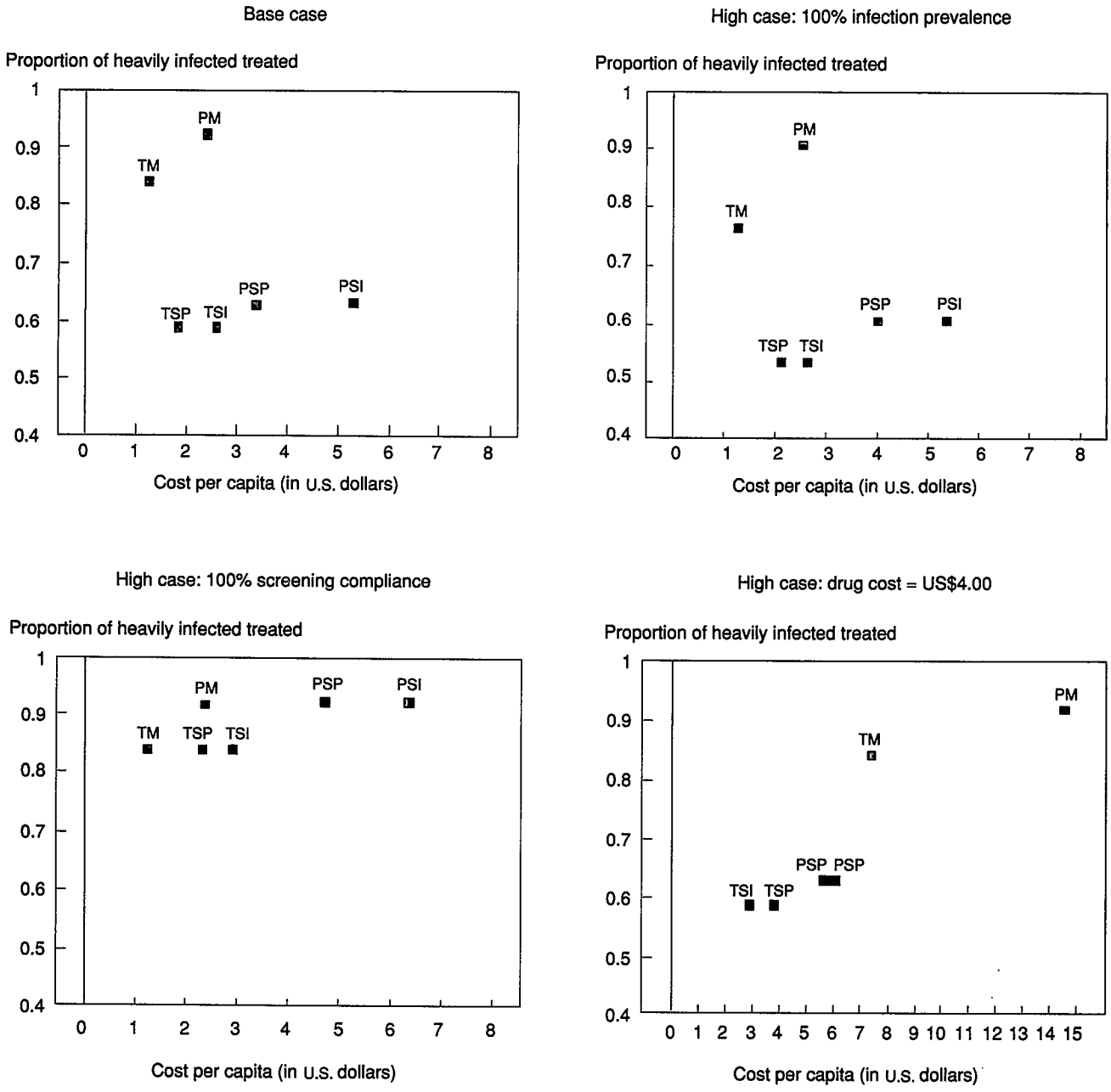
In the presence of a budget constraint, the screening options are not only less effective but also more costly than the mass chemotherapy alternatives. At lower budget levels, targeted mass chemotherapy is both more effective and less costly than targeted screening for prevalence. At higher budget levels, the more effective population mass chemotherapy becomes affordable and always dominates the more costly screening variants. This cost disadvantage of screening options occurs because the slightly lower treatment costs achieved by only treating infected cases are offset by the very high costs of the screening itself. This disadvantage is most acute with the screening for intensity options, which are more costly than the equally effective screening for prevalence options. They have the highest screening costs because of lower technician productivity in assessing specimens for the intensity instead of the mere presence of infection, which implies higher technician and related cost requirements.

In examining the economic factors here and elsewhere in this collection, two standardized populations are considered: one has a low mortality rate and is at an intermediate level of development, and the other has high mortality and birth rates. These demographic differences influence only the overall costs of the various chemotherapy options, the populations with low mortality and low birth rate attracting lower costs because there are proportionately fewer children. The relative position of the different treatment options is unaffected, and the comments in this section apply equally to both types of population.

Increasing prevalence of infection does not change the main results illustrated by the base case. Figure 7-3 also shows the effect of increasing prevalence to 100 percent in both children and adults. The mass chemotherapy options continue to dominate both on effectiveness and on cost-effectiveness criteria. The only consequence of higher prevalence is to lower the effectiveness and raise the cost of all the screening options. In the targeted case this results from the smaller share of children in the total number of heavy infections. The graph in figure 7-3 showing 100 percent infection prevalence reflects the low screening compliance of adults who, in this scenario, have a larger share of the total heavy infections. Thus higher prevalence tends to make mass chemotherapy more attractive.

When screening compliance is raised from the low levels assumed in the base case to the hypothetical maximum of 100 percent both for adults and children, the screening options achieve the same effectiveness as the corresponding mass chemotherapy alternatives. The costs of screening also rise, however, because of the higher volume of postscreening treatment activity. As revealed in the graph showing 100 percent screening compliance in figure 7-3, the implications for optimal choice with a budget constraint are the same as in the base case. Thus even when effectiveness is maximized by the implausible assumption of 100 percent compliance with screening, the cost criteria make screening options unattractive.

Figure 7-3. Cost and Effectiveness of Different Approaches to Community Treatment



Note: Initials refer to the chemotherapy approaches detailed in table 7-12. Effectiveness is measured in terms of the percentage of heavy infections treated. Cost is given in U.S. dollars per person in a population of 1 million, whether or not infected, and are for the total program of two years (six-month cycles of treatment). Base case assumptions are listed in table 7-13.
Source: Authors.

Screening emerges as a preferred strategy only if drug costs are high in relation to screening costs and only in the presence of a budget constraint. The last graph in figure 7-3 illustrates this result in that drug costs are increased to US$4, which simulates the cost of praziquantel for the treatment of schistosomiasis. In this scenario, only the screening options are affordable at lower budget levels, initially on a targeted basis and then on a population basis. At these levels, screening for intensity is less costly than screening for prevalence, although both options are equally effective. At higher budget levels, the more expensive but much more effective mass chemotherapy alternatives become affordable and preferred. An important factor here is that it is only at higher budgetary levels, and only with mass chemotherapy, that an acceptable level of effectiveness is achieved under the present assumptions. Note also that this model assumes a six-month cycle of treatment, whereas,

Table 7-13. Epidemiologic and Behavioral Parameters of the Base Case
(percent)

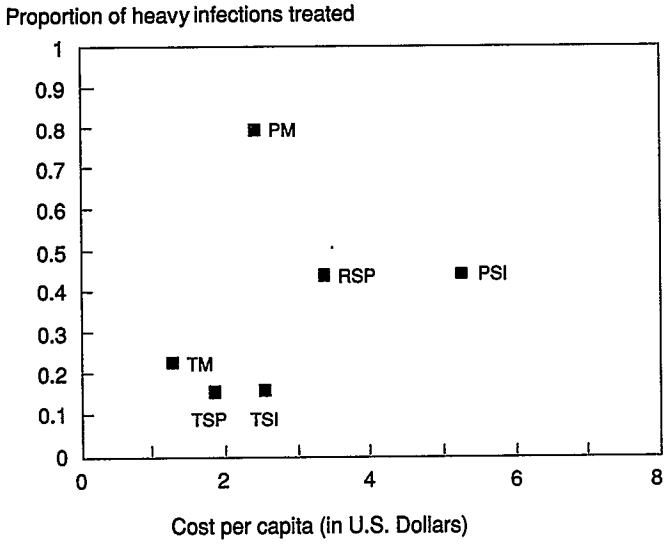
Parameter	Value[a]
Prevalence of infection	
Children	60
Adults	30
Children with heavy infections	15
Percentage of all heavy infections that occur in children	90
Reduction in prevalence due to each cycle of therapy	80
Compliance with treatment	
Children	95
Adults	75
Compliance with screening	
Children	70
Adults	50

a. Values are derived from empirical observation and broadly describe the patterns observed for *Ascaris*, *Trichuris*, and the schistosomes.
Source: Authors.

in practice, chemotherapy against schistosomiasis is delivered on cycles of twelve months or more, which would substantially reduce the costs of all the control programs.

In all the above scenarios we have assumed that intense infection is concentrated in children, as is the case for *Ascaris*, *Trichuris*, and schistosome infections. When it is assumed that intensity of infection rises to an asymptote in young adults, as appears to be the case for hookworm infection, the relative cost-effectiveness of targeted mass chemotherapy is reduced, because it fails to treat the increased share of heavy infections in adults (figure 7-4). Even in this scenario, however, mass chemotherapy is more cost-effective than the screening equivalents. Note also that the age distribution described here is an extreme case and that in reality even hookworm infections may have a high proportion of intense infections in children, a situation that would favor targeted mass chemotherapy.

Figure 7-4. Cost Effectiveness of Various Approaches to Treatment when Intense Infection Occurs in Adults



Note: Abbreviated treatment strategies are described in table 7-12.
Source: Authors.

The main implications of these simulations are the following. First, if there is no budget constraint and the planning objective is simply to maximize the proportion of heavy infections treated, then population mass chemotherapy will always be the optimal intervention. Targeted mass chemotherapy will always be inferior because not all heavy infections occur in children. The higher the proportion of heavy infections in children, however, the greater will be the similarity in effectiveness between population mass and targeted mass chemotherapy. Screening options will generally be inferior because of attrition owing to imperfect screening compliance, but even if compliance were complete, these screening options would only be as good as, but never better than, mass chemotherapy.

Second, if there is a budget constraint the mass chemotherapy options will generally tend to be preferred, with targeted mass chemotherapy at lower budget levels and population mass chemotherapy at higher levels. For infections which tend to be most intense in children (such as *Ascaris*, *Trichuris*, and the schistosomes) the targeted option may provide similar levels of effectiveness to the population option. For infections such as hookworm, where intensity is high in adults, the effectiveness is reduced, although this may be outweighed by the beneficial reduction in morbidity in children.

Third, only in the particular case of drug costs that are high in relation to screening costs, and in the presence of a budget constraint, will screening options be more cost-effective. In these circumstances, higher drug costs will initially favor screening for prevalence, with screening for intensity taking over only when drug costs are high enough to offset the higher costs of screening.

Using the Educational System to Deliver Intervention

The massive prevalence of helminthic infection and the need to deliver treatment to a high proportion of infected individuals impose significant logistic constraints on the design of drug delivery systems. Parasite control programs share with vaccination programs the dubious distinction of being the most extensive health intervention programs ever attempted by humankind. Anthelmintics offer significant logistic advantages over vaccines, however: they are relatively thermostable and do not require a cold chain; they do not have specialized storage requirements; they have an extended shelf life; they do not require technical expertise for administration. Their disadvantage, when compared with most vaccines in current use, is the necessity for repeated delivery, although as discussed above, the putative antihelminth vaccines may require repeated administration and be more costly to deliver than anthelmintics.

The main logistic concern, therefore, is the development of methods to deliver anthelmintics to the community on a regular basis. One solution is to focus drug delivery on school-age children, using the existing educational infrastructure as a delivery mechanism. Treating schoolchildren for worms is not a new idea; it appears to be part of the traditional perception of worm infection in many communities that it is the children who should be treated. Recent research, however, has shown that school-based treatment offers a broad range of advantages, including the potential to achieve community-wide control. In this section we consider school-based treatment as a way of controlling geohelminthiasis and schistosomiasis. We take as given the finding of the preceding subsection that screening is likely to be economically unattractive and that the appropriate strategy will involve mass application to groups targeted by geography and age.

On therapeutic grounds, children are the natural targets for treatment because they tend to have the more intense infections and hence are at greater immediate risk of morbidity. It is now also recognized, however, that disease in childhood has potentially long-term consequences because the peaks of intensity, and thus morbidity, occur at an age which is crucial for physical and intellectual development. Recent studies have shown that the growth of children with intense worm infections may be seriously impaired; furthermore, they have shown that these effects are primarily due to worm infection, because they can be reversed by deworming (Stephenson 1987; Cooper and others 1990). It is particularly significant that deworming alone is sufficient to improve the nutritional status of the children and that great restoration of growth can be achieved without nutritional supplementation. This was graphically illustrated in a recent study showing a remarkable increase in height and weight in children treated for *S. hematobium* infection in Kenya (Stephenson and others 1989a). There is similar evidence that worm infection affects intellectual development (Nokes and others 1992), and the common physical consequences of infection, such as anemia and stunting, are significantly correlated with deficits in cognition and educational measures (Pollitt 1990). The potential effect of helminthiasis on intellectual development is a great cause for concern, because this may prevent children in many developing countries from benefiting from basic education—the only education they may ever receive. The United Nations Educational, Scientific, and Cultural Organization (UNESCO) has undertaken the important new initiative of assessing the effect of helminthiases on the intake of basic education.

Clearly the treatment of school-age children is beneficial in health and developmental terms. Repeated treatment of children also appears to offer benefits to the wider community by reducing the rate of transmission of infection to adults. A school-based chemotherapeutic program in the Caribbean not only achieved a substantial reduction in childhood infection with enteric nematodes, as might be expected, but also reduced infection in adults, less than 4 percent of whom were treated (Bundy and others 1989). It is probable that this effect was due to the significant reduction in contamination by infective stages achieved by removing worms from the heavily infected children, an effect that had been predicted on theoretical grounds (Anderson and May 1982).

It is also now recognized that treatment of children has a long-term developmental effect on the whole community. Physical and intellectual retardation during childhood has consequences for the adult life of the affected individuals. Successful control of parasites in children would, therefore, be expected to provide tangible benefits into the next generation.

Targeting treatment at one specific age group obviously offers significant cost advantages over universal treatment. When the target is schoolchildren these advantages are further increased by the accessibility of the target group (King and others 1989; Wilkins 1989). Schools offer an existing infrastructure for low-cost delivery of anthelmintics and often have established mechanisms for clinical surveillance and community mobilization. They also offer the opportunity for long-term surveillance of randomly selected children with respect to reinfection rates and the effects of treatment of selected parasites on such indexes as height- and weight-for-age and hemoglobin level. Poor school attendance either generally or seasonally may vitiate the effectiveness of this approach.

Cost-Effectiveness of Mass Chemoprophylaxis

Earlier we assessed the economics of screening prior to treatment for various helminthiases and concluded that, for a robust range of assumptions concerning the costs of screening and treatment, mass treatment was a preferable population-based approach to use of diagnostic screening to ascertain which individuals required treatment. Mass treatment, however, could (and should) be targeted to specific geographical regions

Table 7-14. Costs of a Ten-Year School-Based Program Covering 1,000 Children with Chemoprophylaxis for Intestinal Helminthiasis and Schistosomiasis

Component	*Cost (U.S. dollars)*
Praziquantel (4,000 doses)	2,000
Albendazole (8,000 doses)	1,000
Delivery system	5,000–15,000
Total	8,000–18,000
Cost per child	8–18

Note: Program seeks to reach all children age five to fourteen through an annual school visit by a health team. In the ten years of the program, each child should receive praziquantel five times and albendazole ten times. It is assumed, however, that the program is 80 percent effective; on average each child will receive four doses of praziquantel and eight doses of albendazole.

The cost per child contact in WHO's Expanded Programme of Immunization averages about $2.50. That is an upper bound (probably a multiple) of what school-based systems are likely to cost.

The present value of costs would be slightly less than these estimates if costs over the ten-year period were discounted back to the initial year (at 3 percent), as should be done in principle. The effect is small, however, compared with the uncertainty in delivery system costs.

Source: UNICEF 1989.

Table 7-15. Estimated Gains in Healthy Life-Years from a School-Based Program of Chemoprophylaxis for Intestinal Helminthiasis and Schistosomiasis
(years)

Mechanism	Moderate estimate[a]	Low estimate[a]
Reduction in mild-to-moderate schistosomiasis[b]	225	90
Reduction in mild-to-moderate intestinal helminthiasis[b]	225	90
Reduction in heavy schistosomiasis[c]	300	150
Reduction in heavy intestinal helminthiasis[c]	300	150
Reduction in child mortality[d]	125	65
Post-intervention health benefits for target group[e]	150	0
During-intervention benefits for families of target group[f]	150	0
Total	1,475	545

Note: Gains in DALY over a ten-year period in a cohort of 1,000 school-age children, estimated from the program assumptions of table 7-14.

a. Intervention is assumed to result in a gain of 1.2 healthy life-years per year in moderate estimate and 0.1 life-year in low estimate for heavily infected children. Comparable figures for mild to moderate infection are 0.05 and 0.02 life-years.

b. Assumes that 45 percent of children are affected before intervention.

c. Assumes that 15 percent of children are affected before intervention.

d. Assumes 200,000 deaths in all age groups per year from schistosomiasis and all intestinal helminthiases for the low estimate and 400,000 for the moderate; 50 percent of these deaths occur in school-age children in the 40 percent most at risk (in which the cohort of 1,000 students occurs.) These assumptions posit the occurrence of an average of 2.3 deaths over ten years among 1,000 children in the low estimate and 4.6 deaths in the moderate estimate. Discounting at 3 percent from a life expectancy of sixty-five gives the estimates of life-years gained by averting these deaths.

e. In the moderate case, it is assumed that health benefits for each child from the ten-year intervention in the postintervention years would equal 15 percent of the benefits accruing during intervention.

f. In the moderate case, it is assumed that reducing infection in schoolchildren will partially interrupt transmission, thereby reducing morbidity in other members of the children's families. The effect is conservatively assumed to be 15 percent as important as the direct effect on schoolchildren.

Source: Authors.

and age groups. Given the substantially greater intensity of infection among school-age groups than others (figure 7-2), targeting this group becomes a natural priority; the attractiveness of this strategy is further increased by the (relative) logistic and cost attractiveness of intervention through the schools, as was discussed above. Our purpose in this section is to provide an extended hypothetical example of the cost-effectiveness of school-based intervention. Although hypothetical, the cost and effectiveness parameters used are intended to span a reasonable range of probable values; the range of cost-effectiveness estimates is likely, therefore, to provide a realistic sense of what can be achieved.

Given the inevitability of reinfection until high levels of hygiene are ultimately achieved, a strategy based on mass chemoprophylaxis requires periodic, repeated administration of anthelmintics. This is less desirable than prevention achieved through sanitation and hygiene but far less costly. As an interim strategy, therefore, mass chemoprophylaxis is highly cost-effective and, at present, the case is strong for rapid and widespread adoption.

Because of the requirement for repeated drug administration, intervention is best considered as a long-term program. The example we take here assumes a ten-year intervention designed to control schistosomiasis and the intestinal helminthiases in the school-age population (age five to fourteen years). This combination would be appropriate for populations in Northern, Western, and Southern Africa, where a combination of albendazole and praziquantel is used. At low marginal cost, ivermectin could be added to the albendazole and praziquantel used in northern and eastern South America, Central Africa, and Southeast Asia; indeed, given that delivery costs are preponderant among all costs, the cost of serving any of the five groups depicted on the map would vary little from our cost estimates in table 7-14. In the table, we assume a school-based delivery system (probably provided by an annual visit to the school by a mobile team) that serves the entire school-age population. A more detailed discussion of school-based delivery systems for health intervention may be found in Jamison and Leslie (1990). The estimates in table 7-14 suggest that it would be likely to cost between $8.00 and $18.00 per child for a ten-year program (that is, between $0.80 and $1.80 per year) that provided, in that period, four administrations of praziquantel and eight of albendazole. This should control the schistosomes and hookworm very well and *Trichuris* and *Ascaris* moderately well (table 7-11).

Table 7-15 indicates both moderate and low estimates of the benefits of such an intervention for a population of 1,000 school-age children. There is, as shown in the table, a range of benefits; explicit assumptions are made about how these can be expressed in disability-adjusted life-years (DALYs) gained. These assumptions are, in our view, conservative; further, the results (at a broad level) are relatively insensitive to the assumptions. The implications of alternative assumptions, including assumptions about local epidemiology, can easily be assessed.

The cost estimates in table 7-14 and the effectiveness estimates in table 7-15 yield a range of cost-effectiveness estimates from $6 to $33 per DALY gained (table 7-16). Even the high end

Table 7-16. Cost-Effectiveness of a School-Based Program of Chemoprophylaxis for Intestinal Helminthiasis and Schistosomiasis
(U.S. dollars)

Cost per child for ten-year intervention[a]	Cost per disability-adjusted life-year gained	
	Moderate effect[b]	Low effect[b]
8	6	15
18	12	33

a. These costs are the low and high ends of the range reported in table 7-14.

b. The program effect cites the moderate and low estimates for table 7-15.

Source: Authors.

of this range of costs is relatively attractive—comparable to diphtheria-pertussis-tetanus (DPT)-plus-polio immunization (Jamison and others, chapter 6, this collection). At the low end of the range, the intervention becomes one of the most cost-effective means of promoting child health.

It is, in this context, worth recalling the estimates of cost-effectiveness of several preventive interventions that were previously presented. Although applicable in only limited foci, improved water supply to control dracunculiasis is also highly cost-effective—perhaps $25 per healthy life-year gained. Vector control for prevention of onchocerciasis is far less attractive at perhaps $300 per healthy life-year gained.

Priorities and Conclusion

The availability of a series of broad-spectrum anthelmintics which have minimal side effects and are administered orally in a single dosage has begun to be widely appreciated. Coupled with the unique biology, ecology, and epidemiology of the macroparasites (helminths) as compared with microparasites (viruses, bacteria, protozoa), these new anthelmintics allow a strategy of controlling disease, rather than infection, by maintaining worm burdens at low levels via chemoprophylaxis. How best the new drugs can be employed, with what effect, and at what cost are all questions which are beginning to be addressed. An important question is that, although the helminthiases are the most widespread infections in the developing world, is their control warranted in so many countries which today are operating under severe budget constraints and in an environment where prospects for significant assistance from donors for any health program are discouraging? The introduction of any new health intervention has to be weighed carefully, as to both the benefits and the costs, as well as to the prospects for obtaining needed resources.

Available data, as reviewed in this chapter, document the prevalence of helminthic infections, usually with several being present simultaneously. Substantial improvements in control through prevention is not an option in the short to medium term without unrealistically large investments in sanitation or vector control. (Dracunculiasis provides an important exception to this generalization; preventive measures appear both cost-effective and capable of eradicating the disease during the 1990s.) For the foreseeable future, therefore, chemotherapy is the dominant option in most countries. Traditional practice would call for evaluating the new chemotherapeutic agents by their ability to cure diagnosed infections in individuals. Diagnosis and treatment of infection in individuals, however, are not only costly procedures, but their application is beyond the capacity of most health services. Moreover, where infection is rife, amelioration of disease symptoms is apt to be of short duration because of rapid reinfection.

Given the fact that infections in many areas are so widespread, although not infrequently asymptomatic, alternative practices should be considered with two objectives in mind: to diminish the incidence of symptomatic infection and to provide for large-scale treatment without costly and time-consuming diagnostic procedures. The administration of lower dosages of certain of the drugs might reduce or eliminate symptoms without necessarily drastically reducing efficacy. Use of lower dosages might also be less costly.

The design, implementation, and evaluation of treatment regimens are complicated by the fact that most individuals in the tropics are infected with not one but several helminths. Symptomatic manifestations, not surprisingly, usually represent a cumulative burden of the effects of multiple infections. Studies which dissect out the proportionate contributions to illness of the different helminths are few indeed and often difficult to interpret. Even if done, it would be impossible to generalize results from one geographic area to another, given the array of variables which are present.

Given this quandary, and the immense global burden of multiple helminthic infection, it would be worthwhile to consider pilot programs in which two or even three chemotherapeutic agents are administered concomitantly at periodic intervals and on a large scale to selected population groups to evaluate the cost and effectiveness of such programs in diminishing symptomatic disease. Available data suggest that such programs should be cost-effective, but confirmation is required. Such a strategy would be consonant with a transformation which has begun to occur in the provision of a number of health services in developing countries. Community-wide programs for vaccination, oral rehydration therapy, vitamin A supplementation, and family planning have been growing in number and extent, proving to be far more effective than programs directed solely to individuals who present themselves at health centers or hospitals. Such community-based programs, directed to the control of helminthic diseases, have only begun to be explored but, where conducted, they have proved to be most successful. Community-wide programs for anthelmintic drug administration might be targeted at school-age children, for example, and be conducted simultaneously or at least in concert with other community-based programs for vitamin A administration or vaccination, at marginal additional cost.

Programs are needed to determine with certainty that two or three anthelmintic agents can be given concomitantly or within a circumscribed time period with safety and without loss of efficacy. Mechanisms for involving, motivating, and educating effectively the populations concerned are required, as they are with other community-based programs. High-risk populations requiring treatment would need to be identified. This could be done inexpensively by sample surveys rather than by a total screening of the population. Evaluation of selected regimens—for example, mass treatment of school-age children yearly—could be conducted in a similar manner.

The important departure, however, is to conceptualize the potential use and evaluation for these new chemotherapeutic agents in a new framework. Given their cost, particularly where therapeutic doses that are lower than usual could be employed, and given the burden of helminthic infection, large-

scale mass treatment could represent an important and cost-effective health strategy in many parts of the world where improved sanitation and vector control are not presently feasible. Estimates of cost-effectiveness suggest that measures of this sort are likely to prove attractive within the present range of options for improving child health.

Notes

Preparation of this chapter was supported financially by the World Bank and by Global Health Partners, Inc. The views expressed do not, of course, necessarily reflect those of the sponsoring organizations. The authors wish to express their gratitude to the following individuals for valuable advice and comments on earlier drafts: J. Cook, C. Cruz, D. Evans, T. Evans, R. Feachem, D. Hopkins, J.-L. Lamboray, W. H. Mosley, M. Percopo, A. Seim, G. Torrigiani, and S. Van der Vynckt.

References

Albers-Schoenberg, G., B. H. Arison, J. C. Chabala, A. W. Douglas, P. Eskola, M. H. Fisher, A. Lusi, H. Mrozik, F. L. Smith, and R. L. Tolman. 1981. "Avermectins: Structure Determination." *Journal of the American Chemical Association* 102:4216–21.

Albiez, E. J., G. Walter, A. Kaiser, P. Ranque, H. S. Newland, A. T. White, B. M. Greene, H. R. Taylor, and D. W. Buttner. 1988. "Histological Examination of Onchocercomata after Therapy with Ivermectin." *Tropical Medicine Parasitology* 39:93–99.

Anderson, R. M. 1982. *Population Dynamics of Infectious Diseases: Theory and Applications*. London: Chapman and Hall.

———. 1986. "The Population Dynamics and Epidemiology of Intestinal Nematode Infections." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 686–96.

———. 1987. "Determinants of Infection in Schistosomiasis." *Clinical Tropical Medicine and Communicable Diseases* 2:279–300.

———. 1988. "Determinants of Infection in Human Schistosomiasis." *Clinical Tropical Medicine and Communicable Diseases* 2:279–300.

———. 1989. "Transmission Dynamics of *Ascaris lumbricoides* and the Impact of Chemotherapy." In D. W. T. Crompton, M. C. Nesheim & Z. S. Pawlowski, eds., *Ascariasis and Its Prevention and Control*. London: Taylor and Francis.

Anderson, R.M. and R.M. May. 1982. "Population Dynamics of Human Helminth Infections: Control by Chemotherapy." *Nature* 297:557–63.

———. 1985. "Helminth Infections of Humans: Mathematical Models, Population Dynamics and Control." *Advances in Parasitology* 1–101.

Anderson, R. M., R. M. May, and S. Gupta. 1989. "Non-linear Phenomena in Host-Parasite Interactions." *Parasitology* 99:S59–S79.

Anderson, R. M. and G. F. Medley. 1985. "Community Control of Helminth Infections of Man by Mass and Selective Chemotherapy." *Parasitology* 90:629–60.

Andreano, R., and T. Helminiak. 1988. "Economics, Health and Tropical Disease: A Review." In H. N. Herrin, and P. Rosenfield, eds., *Economics, Health and Tropical Diseases*. Manila: University of the Philippines, School of Economics.

Arfaa, F. 1986. "Ascariasis and Trichuriasis." In J. A. Walsh and K. S. Warren, eds., *Strategies for Primary Health Care*. Chicago: University of Chicago Press.

Barbour, A. D. 1982. "Schistosomiasis." In R.M. Anderson, ed., *Population Dynamics of Infectious Diseases: Theory and Applications*. London: Chapman and Hall.

Behm, C. A., and C. Bryant. 1985. "The Modes of Action of Some Modern Anthelmintics." In Anderson and Waller, eds. *Resistance in Nematodes to Anthelmintic Drugs*. Glebe, Australia: CSIRO Publication.

Borgers, M., S. De Nollin, A. Verheyen, M. De Brabander, and D. Thienpont. 1975. "Influence of the Anthelmintic Mebendazole on Microtubules and Intracellular Organelle Movement in Nematode Intestinal Cells." *American Journal of Veterinary Research* 36:1153–66.

Bradley, D. J., and F. S. McCullough. 1974. "Egg Output Stability and the Epidemiology of *Schistosoma haematobium*." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 80:706–18.

Bundy, D. A. P. 1986. "Epidemiological Aspects of *Trichuris* and Trichuriasis in Caribbean Communities." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 80:706–18.

———. 1988. "Population Ecology of Intestinal Helminth Infections in Human Communities." *Philosophical Transactions of the Royal Society of London* 321:405–20.

Bundy, D. A. P., and U. Blumenthal. 1989. "The Impact of Human Behaviour on the Epidemiology of Schistosomiasis and Geohelminthiasis." In G. Bernard and J. Behnke, eds., *Behaviour and Parasitism*. London: Taylor and Francis.

Bundy, D. A. P., and E. S. Cooper. 1989. "Trichuris and Trichuriasis in Humans." *Advances in Parasitology*, 28:107–73.

Bundy, D. A. P., E. S. Cooper, D. E. Thompson, R. M. Anderson, and J. M. Didier. 1987. "Age-related Prevalence and Intensity of *Trichuris trichiura* Infection in a St. Lucian Community." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 81:85–94.

Bundy, D. A. P., S. P. Kan, and R. Rose, and others. 1988a. "Age-related Prevalence, Intensity and Frequency of Distribution of Gastrointestinal Helminth Infections in Urban Slum Children from Kuala Lumpur, Malaysia." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 82:289–94.

Bundy, D. A. P., E. S. Cooper, D. E. Thompson, J. M. Didier, and I. Simmons. 1988b. "Effect of Age and Initial Infection Status on the Rate of Reinfection with *T. trichiura* after Treatment." *Parasitology* 97:469–76.

Bundy, D. A. P., E. S. Cooper, D. E. Thompson, J. M. Didier, R. M. Anderson, and I. Simmons. 1988c. "Predisposition to *Trichuris trichiura* Infection in Humans." *Epidemiology and Infection* 98:65–71.

Bundy, D. A. P., D. E. Thompson, E. S. Cooper, M. H. N. Golden, and R. M. Anderson. 1985. "Population Dynamics and Chemotherapeutic Control of *Trichuris trichiura* Infection of Children in Jamaica and St. Lucia." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 69: 759–64.

Bundy, D. A. P., M. S. Wong, L. L. Lewis and J. Horton. 1989. "Control of Gastro-intestinal Helminths by Age-Group Targeted Chemotherapy Delivered through Schools." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 8:115–20.

Cabrera, B. D., B. Caballero, L. Rampal, and W. de Leon. 1989. "The Philippines." In D. W. T. Crompton, M. C. Nesheim, and Z. S. Pawlowski, eds., *Ascariasis and Its Prevention and Control*. London: Taylor and Francis.

Cairncross, A. C., and R. G. Feachem. 1983. *Environmental Health Engineering in the Tropics*. Chichester, U.K.: John Wiley and Sons.

Campbell, W. C., M. H. Fisher, E. O. Stapley, G. Albers-Schoenberg, and T. A. Jacob. 1983. "Ivermectin: A Potent New Antiparasitic Agent." *Science* 221:823–28.

Chandler, A. C. 1925. "The Rate of Loss of Hookworms in the Absence of Reinfections." *Indian Journal of Medical Research* 13:625–34.

CIBA Foundation. 1987. *Filariasis*, ed. D. Everard and S. Cook. Chichester, U.K.: John Wiley and Sons.

Cook, J. A. 1987. "Strategies for Control of Human Schistosomiasis." *Clinical Tropical Medicine and Communicable Diseases* 2:449–63.

Cook, J. A., P. Jordan, and P. Armitage. 1976. "Hycanthone Dose-Response in Treatment of Schistosomiasis Mansoni in St. Lucia." *American Journal of Tropical Medicine and Hygiene* 25:602–7.

Cooper, E. S., and D. A. P. Bundy. 1986. "Trichuriasis." In A. S. McNeish and J. A. Walker-Smith, eds., *Diarrhoea and Malnutrition in Childhood*. London: Buttersworth.

———. 1987. "Trichuriasis: In Intestinal Helminthic Infections." *Baillière's Clinical Tropical Medicine and Communicable Diseases* 2:629–43.

———. 1988. "Trichuris Is Not Trivial." *Parasitology Today* 4:301–6.

Cooper, E. S., D. A. P. Bundy, and F. S. Henry. 1986. "Chronic Dysentery, Stunting, and Whipworm Infestation." *Lancet* (August 2):280–81.

Cooper, E. S., D. A. P. Bundy, T. T. Macdonald, and M. H. N. Golden. 1990. "Growth Suppression in the *Trichuris* Dysentery Syndrome." *European Journal of Clinical Nutrition* 44:138–47.

Cort, W. W. 1922. "A Graphic Analysis of Certain Factors in Hookworm Control." *American Journal of Tropical Medicine* 2:449–63.

Croll, N. A., R. M. Anderson, T. W. Gyorkos, and E. Ghadirian. 1982. "The Population Biology and Control of *Ascaris lumbricoides* in a Rural Community in Iran." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 76:187–97.

Crompton, D. W. T. 1985. "Chronic Ascariasis and Malnutrition." *Parasitology Today* 1:47–52.

———. 1989. "The Prevalence of Ascariasis." In D. W. T. Crompton, M. C. Nesheim, and Z. S. Pawlowski, eds., *Ascariasis and Its Prevention and Control*. London: Taylor and Francis.

Cupp, E. W., A. O. Ochoa, R. C. Collins, F. R. Ramberg, and G. Zea. 1989. "The Effect of Multiple Ivermectin Treatments on Infection of *Simulium ochraceum* with *Onchocerca volvulus*." *American Journal of Tropical Medicine and Hygiene* 40:501–6.

Dadzie, K. Y., A. C. Bird, K. Awadzi, H. Schulz-Key, H. M. Gilles, and M. A. Aziz. 1987. "Ocular Findings in a Double-Blind Study of Ivermectin versus Diethylcarbamazine versus Placebo in the Treatment of Onchocerciasis." *British Journal of Ophthalmology* 71:78–85.

Davis, Andrew. 1986. "Available Anthelmintics and Future Needs." In H. Machleidt, ed., *Contributions of Chemistry to Health: Proceedings of the Fifth CHEMRAWN Conference*, vol. 2. Wernheim, Fed. Rep. Germany: VCH Verlagsgesellischaft mbH.

———. 1989. "Chemotherapy: Options for Delivery Systems." In Max J. Miller and E. J. Love, eds., *Parasitic Diseases: Treatment and Control*. Boca Raton, Fla.: CRC Press.

Degremont, A., G. K. Lwihula, C. Mayombana, E. Burnier, D. de Savigny, and M. Tanner. 1987. "Longitudinal Study on the Health Status of Children in a Rural Tanzanian Community: Parasitoses and Nutrition Following Control Measure against Intestinal Parasites." *Acta Tropica* 44:175–90.

Dietz, Klaus. 1982. "The Population Dynamics of Onchocerciasis." In R. M. Anderson, ed., *Population Dynamics of Infectious Diseases: Theory and Applications*. London: Chapman and Hall.

Edungbola, L. D., S. J. Watts, T. O. Alabi, and A. B. Bello. 1988. "The Impact of a UNICEF-Assisted Rural Water Project on the Prevalence of Guinea Worm Disease in Asa, Kwara State, Nigeria." *American Journal of Tropical Medicine and Hygiene* 39:79–85.

Egerton, J. R., D. Suhayda, and C.H. Eary. 1988. "Laboratory Selection of *Haemonchus contortus* for Resistance to Ivermectin." *Journal of Parasitology* 74:614–17.

el Karim, M. A., K. J. Collins, J. R. Brotherhood, C. Dore, J. S. Weiner, M. Y. Sukkar, A. H. Omer, and M. A. Amin. 1980. "Quantitative Egg Excretion and Work Capacity in a Gezira Population Infected with *Schistosoma mansoni*." *American Journal of Tropical Medicine and Hygiene* 29:54–61.

Elkins, D. B., M. Haswell-Elkins, and R. M. Anderson. 1986. "The Epidemiology and Control of Intestinal Helminths in the Pulicat Lake Region of Southern India: Study Design and Pre- and Post-treatment Observations on *Ascaris lumbricoides* Infection." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 80:774–92.

Evans, T. G., and C. J. L. Murray. 1987. "A Critical Re-examination of Blindness Prevention under the Onchocerciasis Control Programme." *Social Science and Medicine* 25:241–49.

Feachem, R. G. A., D. J. Bradley, H. Garelick, and D. D. Mara. 1983a. *Sanitation and Disease*. Chichester, U.K.: John Wiley and Sons.

Feachem, R. G. A., M. W. Guy, S. Harrison, K. O. Wugo, T. Marshall, N. Mbere, R. Muller, and A. M. Wright. 1983b. "Excreta Disposal Facilities and Intestinal Parasitism in Urban Africa: Preliminary Studies in Botswana, Ghana and Zambia." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 77:515–21.

Fisher, M. H., and H. Mrozik. 1989. "Chemistry." In W. C. Campbell, ed., *Ivermectin and Abamectin*. New York: Springer Verlag.

Fosdick, R. 1952. *The Story of the Rockefeller Foundation*. New York: Harper & Brothers.

Gemmell, M. A., J. R. Lawson, and M. G. Roberts. 1986. "Control of Echinococcosis/Hydatidosis: Present Status of World-Wide Progress." *Bulletin of the World Health Organization* 64:333–39.

Greene, B. M., K. R. Brown, and H. R. Taylor. 1989. "Use of Ivermectin in Humans." In W. C. Campbell, ed., *Ivermectin and Abamectin*. New York: Springer Verlag.

Grove, D. 1989. *Strongyloidiasis*. London: Taylor and Francis.

Hairston, N. G. 1965. "On the Mathematical Analysis of Schistosome Populations." *Bulletin of the World Health Organization* 33:45–62.

Harpham, T., T. Lusty, and P. Vaughan. 1987. *In the Shadow of the City: Community Health and the Urban Poor*. Oxford: Oxford University Press.

Hayashi, S. 1980. "Economic Loss from Parasites." *Collected Papers on the Control of Soil-Transmitted Helminthiases*. Tokyo: Asian Parasite Control Organization.

Hill, R. B. 1926. "The Estimation of the Number of Hookworms Harboured, by the Use of the Egg Dilution Method." *American Journal of Tropical Medicine and Hygiene* 6:19–41.

Holland, C. V. 1987a. "Hookworm Infection." In L. S. Stephenson, ed., *Impact of Helminth Infections on Human Nutrition*. London: Taylor and Francis.

———. 1987b. "Neglected Infections—Trichuriasis and Strongyloidiasis." In L.S. Stephenson, ed., *Impact of Helminth Infections on Human Nutrition*. London: Taylor and Francis.

Hopkins, D. R., and E. Ruiz-Tiben. 1990. *Dracunculiasis Eradication: Target 1995*. Atlanta: Carter Center. *American Journal of Tropical Medicine and Hygiene*. 43:296–300

Ilegbodu, V. A., O. O. Kale, R. A. Wise, B. L. Christensen, J. H. Steele, and L. A. Chambers. 1986. "Impact of Guinea Worm Disease on Children in Nigeria." *American Journal of Tropical Medicine and Hygiene* 35:962–94.

Ismid, I. S., and B. Rukmono. 1980. "The Effect of Latrine Provision and Health Education on Soil Pollution." In *Collected Papers on the Control of Soil-Transmitted Helminthiases*, vol. 1. Tokyo: Asian Parasite Control Organization.

Jamison, D. T., and J. Leslie. 1990. "Health and Nutrition Considerations in Educational Planning: The Cost and Effectiveness of School-based Intervention." *Food and Nutrition Bulletin* 12:204–14.

Kan, S. P., H. L. Guyatt, and D. A. P. Bundy. 1989. "Geohelminth Infection of Children from Rural Populations and Urban Slums in Malaysia." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 83:817–21.

Kass, I. S., A. O. W. Stretton, and C. C. Wang. 1984. "The Effects of Avermectin and Drugs Related to Acetylcholine and 4-aminobutyric Acid on Neurotransmission in *Ascaris suum*." *Molecular and Biochemical Parasitology* 13:213–25.

Kass, I. S., C. C. Wang, J. P. Walrond, and A. O. W. Stretton. 1980. "Avermectin B_{1a}, a Paralyzing Anthelminthic that Affects Interneurons

and Inhibitory Motor Neurons in *Ascaris*." *Proceedings of the National Academy of Science* 77:6211–15.

Kilama, W. L. 1989. "Sanitation in the Control of Ascariasis." In D. W. T. Crompton, M. C. Nesheim, and Z. S. Pawlowski, eds., *Ascariasis and Its Prevention and Control*. London: Taylor and Francis.

King, C. A., D. W. Wiper, K. V. Destigter, P. A. S. Peters, D. Koech, J. H. Ouma, T. K. A. Siongok, and A. A. F. Mahmoud. 1989. "Dose-finding Study for Praziquantel Therapy of *Schistosoma hematobium* in Coast Province, Kenya." *American Journal of Tropical Medicine and Hygiene* 40:507–13.

Kumaraswami, V., E. A. Ottesen, V. Vijayasekaran, S. Uma Devi, M. Swaminathan, M. A. Aziz, G. R. Sarma, R. Prabhakar, and S. P. Tripathy. 1988. "Ivermectin for the Treatment of *Wuchereria bancrofti* Filariasis: Efficacy and Adverse Reactions." *JAMA* 259:3150–53.

Kvalsvig, J. D. 1988. "The Effects of Parasitic Infection on Cognitive Performance." *Parasitology Today* 4:206–8.

Lacey, E. 1986. "The Biochemistry of Anthelmintic Resistance." In Anderson and Waller, eds., *Resistance in Nematodes to Anthelmintic Drugs*. Glebe, Australia: Commonwealth Scientific and Industrial Research Organization.

Lemma, A. 1987. "Overview of Endod Studies." In *Endod II: Report of the Second International Workshop on Endod*. New York: UNICEF CIPA.

Le Riche, W. H. 1967. "World Incidence and Prevalence of the Major Communicable Diseases." In G. Wolstenholme and M. O'Connor, eds., *Health of Mankind*. London: J. and A. Churchill.

Levin, N. 1988. "Controlling Iron-Binding Deficiency Anemia: A Cost-Benefit Analysis." *World Health* 27–29.

Lok, J. B., T. Harpaz, and D. H. Knight. 1988. "Abnormal Patterns of Embryogenesis in *Dirofilaria immitis* Treated with Ivermectin." *Journal of Helminthology* 62:175–80.

McGarvey, S. T., B. L. Daniel, M. Tso, G. Wu, S. Zhong, R. Olveda, P. M. Wiest, and G. R. Olds. 1990. "Child Growth and Schistosomiasis Japonica in the Philippines and China." Paper presented at the meeting of the American Society for Clinical Investigation, Washington, D.C. *Clinical Research* 38.

Migasena, S., and H. M. Gilles. 1987. "Hookworm Infections." *Clinical and Tropical Medicine and Communicable Diseases* 2:617–27.

Miller, T. A. 1978. "Industrial Development and Field Use of the Canine Hookworm Vaccine." *Advances in Parasitology* 16:333–42.

Morishita, K. 1980. "Japanese Literatures Concerning Influence of Parasites, Especially of Soil-Transmitted Helminths upon the Psychosomatic Condition in Maternity and Childhood." In *Collected Papers on the Control of Soil-Transmitted Helminthiases*. Tokyo: Asian Parasite Control Organization.

Morrow, R. H. 1984. "The Application of a Quantitative Approach to the Assessment of the Relative Importance of Vector and Soil-Transmitted Diseases in Ghana." *Social Sciences and Medicine* 19:1039–49.

Mossinger, J., H. Schulz-Key, and K. Dietz. 1988. "Emergence of *Onchocerca volvulus* Microfilaria from Skin Snips before and after Treatment of Patients with Ivermectin." *Tropical Medicine and Parasitology* 39:313–16.

Mott, K. E. 1988. "Schistosomiasis Control." In D. Rollinson and A. Simpson, eds., *The Biology of Schistosomes*. London: Academic Press.

Mrozik, H., P. Eskola, M. H. Fisher, J. R. Egerton, S. Cifelli, and D. A. Ostlind. 1982. "Avermectin Acyl Derivatives with Anthelminthic Activity." *J. Med. Chem.* 25:658–63.

Naquira, C., G. Jiminez, J. G. Guerra, R. Bernal, D. R. Nalin, D. Neu, and M. Aziz. 1989. "Ivermectin for Human Strongyloidiasis and Other Intestinal Helminths." *American Journal of Tropical Medicine and Hygiene* 40:304–9.

Newland, H. S., A. T. White, B. M. Greene, S. A. D'Anna, E. Keyvan-Larijani, M. A. Aziz, P. N. Williams, and H. R. Taylor. 1988. "Effect of Single-dose Ivermectin Therapy on Human *Onchocerciasis volvulus* Infection with Onchocercal Ocular Involvement." *British Journal of Ophthalmology* 72:561–69.

Nokes, C., S. M. Grantham-McGregor, A. W. Sawyer, E. S. Cooper, and D. A. P. Bundy. 1992. "Helminth Infection and Cognitive Function." Proceedings of the Royal Society (London) 247:77–81.

Ottesen, E. A., V. Vijayasekaran, V. Kumaraswami, S. V. Perumal Pillai, A. Sadanandam, S. Frederick, R. Prabhakar, and S. P. Tripathy. 1990. "A Controlled Trial of Ivermectin and Diethylcarbamazine in Lymphatic Filariasis." *New England Journal of Medicine* 322:1113–18.

Otto, G. F., W. W. Cort, and A. E. Keller. 1931. "Environmental Studies of Families in Tennessee Infested with Ascaris, Trichuris, and Hookworm." *American Journal of Hygiene* 14:156–93.

Partono, F. 1985. "Diagnosis and Treatment of Lymphatic Filariasis." *Parasitology Today* 1:52–57.

Partono, F., Purnomo, and A. Soewarta. 1979. "A Simple Method to Control *Brugia timori* by Diethylcarbamazine Administation." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 73:536–42.

Paul, J. E., R. B. Isley, and G. M. Ginsberg. 1986. "Cost-Effective Approaches to the Control of Dracunculiasis." WASH Technical Report 38. USAID Office of Health, Washington, D.C.

Pawlowski, Z. S. 1984. "Ascariasis." *Annales de la Société Belge de Médicine Tropicale* 64:125–34.

Pawlowski, Z. S., and A. Davis. 1989. "Morbidity and Mortality in Ascariasis." In D. W. T. Crompton, M. C. Nesheim, and Z. S. Pawlowski, eds., *Ascariasis and Its Prevention and Control*. London: Taylor and Francis.

Peters, W. 1978. "The Relevance of Parasitology to Human Welfare Today." *Symposium of the British Society of Parasitology* 16:25–40.

Polderman, A. M., B. Gryseels, and P. DeCaluwe. 1988. "Cure Rates and Egg Reduction in Treatment of Intestinal Schistosomiasis with Oxamniquine and Praziquantel in Maniema, Zaire." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 82:115–16.

Pollitt, E. 1990. *Malnutrition and Infection in the Classroom*. Paris: UNESCO.

Pollitt, E., P. Hathirat, P., and N. J. Kotchabharkdi. 1989. "Iron Deficiency and Educational Achievement in Thailand." *American Journal of Clinical Nutrition* 50:687–97.

Prescott, N. M. 1979. "Schistosomiasis and Development." *World Development* 7:1–14.

———. 1987. "The Economics of Schistosomiasis Chemotherapy." *Parasitology Today* 3:21–24.

———. 1989. "Economic Analysis of Schistosomiasis Control Projects." In M. W. Service, ed., *Demography and Vector-borne Diseases*. Boca Raton, Fla.: CRC Press.

Prescott, N. M., and M. F. Jancloes. 1984. "The Analysis and Assessment of Health Programs." *Social Science and Medicine* 19:1057–60.

Prichard, R. K. 1970. "Mode of Action of the Anthelmintic Thiabendazole in *Haemonchus contortus*." *Nature* 228:584–85.

Prost, A. and N. Prescott. 1984. "Cost Effectiveness of Blindness Prevention by the Onchocerciasis Control Programme in Upper Volta." *Bulletin of the World Health Organization* 62:795–802.

Rajagopalan, P. K., P. K. Das, S. Subramanian, P. Vanamail, and K. D. Ramaia. 1989. "Control of Bancroftian Filariasis in Pondicherry, South India. Pre-control Epidemiological Observations." *Epidemiology and Infection* 103:685–92.

Richard-Lenoble, D., M. Kombila, E. A. Rupp, E. S. Papayliuo, P. Gaxotte, C. Nguiri, and M. A. Aziz. 1988. "Ivermectin in Loiasis and Concomitant O. *volvulus* and M. *perstans* Infections." *American Journal of Tropical Medicine and Hygiene* 39:480–83.

Rim, H. J. 1986. "The Current Pathobiology and Chemotherapy of Clonorchiasis." *Korean Journal of Parasitology* 24:1–141.

Rosenfield, P. L., F. Galladay, and R. K. Davidson. 1984. "The Economics of Parasitic Diseases: Research Priorities." *Social Science and Medicine* 19:117–126.

Sasa, M. 1977. *Human Filariasis: A Global Survey of Epidemiology and Control.* Tokyo: University of Tokyo Press.

Schad, G. A., and K. S. Warren. 1989. *Hookworm Infection: Current Status and New Directions.* London: Taylor and Francis.

Seim, A. R. 1990. *Guinea Worm Disease Eradication Project.* Fagerstrand, Norway: Health and Development International.

Smillie, W. G. 1924. "Control of Hookworm Disease in South Alabama." *Southern Medical Journal* 17:494–99.

Smith, G. S., D. Blum, S. R. A. Huttly, N. Okeke, B. R. Kirkwood, and R. G. A. Feachem. 1989. "Disability from Dracunculiasis: Effect on Mobility." *Annals of Tropical Medicine and Parasitology* 83:151–58

Soboslay, P. T., H. S. Newland, A. T. White, K. D. Erttmann, E. J. Albiez, H. R. Taylor, P. N. Williams, and B. M. Greene. 1987. "Ivermectin Effect on Microfilaria of *Onchocerca volvulus* after a Single Oral Dose in Humans." *Trop.Med.Parasitol.* 39:8–10.

Soderlund, D. M., P. M. Adams, and J. R. Bloomquist. 1987. "Difference in the Action of Avermectin B1a on the GABA Receptor Complex of Mouse and Rat." *Biochemical and Biophysical Research Communications* 146:692–98.

Stephenson, L. S. 1987. *Impact of Helminth Infections on Human Nutrition.* London: Taylor and Francis.

Stephenson, L. S., M. C. Latham, K. M. Kurz, and S. N. Kinotti. 1989a. "Single Dose Metrifonate or Praziquantel Treatment in Kenyan Children. Effects on Growth in Relation to *Schistosoma hematobium* and Hookworm Egg Counts." *American Journal of Tropical Medicine and Hygiene* 41: 445–53.

Stephenson, L. S., M. C. Latham, K. M. Kurz, S. N. Kinoti, and H. Brigham. 1989b. "Treatment with a Single Dose of Albendazole Improves Growth of Kenyan Schoolchildren with Hookworm, *Trichuris trichiura*, and *Ascaris lumbricoides* Infections." *American Journal of Tropical Medicine and Hygiene* 41:78–87.

Stephenson, L. S., S. N. Kinoti, K. M. Kurz, and H. Brigham. 1990. "Improvements in Physical Fitness of Kenyan Schoolboys Infected with Hookworm, *Trichuris trichuria* and *Ascaris lumbricoides* Following a Single Dose of Albendazole." *Transactions of the Royal Society for Tropical Medicine and Hygiene* 84:277–82.

Stoll, N. R. 1947. "This Wormy World." *Journal of Parasitology* 33:1–18.

Taylor, H. R., R. D. Semba, H. S. Newland, E. Keyvan-Larijani, A. White, Z. Dukuly, and B. M. Greene. 1989. "Ivermectin Treatment of Patients with Severe Ocular Onchocerciasis." *American Journal of Tropical Medicine and Hygiene* 40:494–500.

Taylor, P., H. M. Murure, K. Manomano. 1988. "Efficacy of Low Doses of Praziquantel for *Schistosoma mansoni* and *S. haematobium.*" *Journal of Tropical Medicine and Hygiene* 91:13–17.

Terry, C., D. A. P. Bundy, and J. Horton. 1989. "Relative Costs of Targeted, Selective, and Selected Chemotherapeutic Control of Geohelminths." PERG/SKF. Mimeo.

Turner, M. J., and J. M. Schaeffer. 1989. "Mode of Action of Ivermectin." In W. C. Campbell, ed., *Ivermectin and Avermectin.* New York: Springer Verlag.

UNICEF (United Nations Childrens Fund). 1989. *Essential Drugs Price List.* Copenhagen: Supply Division.

Wakelin, D. 1978. "Immunity to Intestinal Parasites." *Nature* 273:617–20.

Walsh, J. A. 1990. "Estimating the Burden of Illness in the Tropics." In K. S. Warren and A. A. F. Mahmoud, eds., *Tropical and Geographical Medicine.* New York: McGraw-Hill.

Walsh, J. A., and K. S. Warren. 1979. "Selective Primary Health Care: An Interim Strategy for Disease Control in Developing Countries." *New England Journal of Medicine* 301:967–74.

Warren, K. S. 1973. "Regulation of the Prevalence and Intensity of Schistosomiasis in Man: Immunology or Ecology?" *Journal of Infectious Diseases* 127:595–609.

———. 1989. "Selective Primary Health Care and Parasitic Diseases in McAdam, KPR." In K. P. R. McAdam, ed., *New Strategies in Parasitology.* London: Churchill Livingstone.

Warren, K.S., and A. A. F. Mahmoud. 1990. *Tropical and Geographical Medicine.* 2d ed. New York: McGraw Hill.

Warren, K. S., J. H. Ouma, T. Arap Siongok, and H. B. Houser. 1978. "Hycanthone Dose-Response in *Schistosoma mansoni* Infection in Kenya." *Lancet* 1:352–54.

WHO (World Health Organization). 1980. *Sixth Report on the World Health Situation.* Part 1, *Global Analysis.* Geneva.

———. 1985. "The Control of Schistosomiasis." Technical Report Series 728. Geneva.

———. 1987a. *Atlas of the Global Distribution of Schistosomes.* Geneva.

———. 1987b. "Prevention and Control of Intestinal Parasitic Infections." Technical Report Series 749. Geneva.

Wilkins, H. A. 1989. "Reinfection after Treatment of Schistosome Infections." *Parasitology Today* 3:83–88.

Yekutiel, P. 1980. "Eradication of Infectious Diseases." In M. A. Klinsberg, ed., *Contributions to Epidemiology and Biostatistics,* vol. 2. Basel: Karger.

Young, M. E., and A. Prost. 1985. "Child Health in China." World Bank Staff Working Paper. Washington, D.C.